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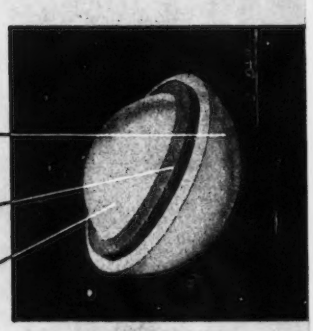

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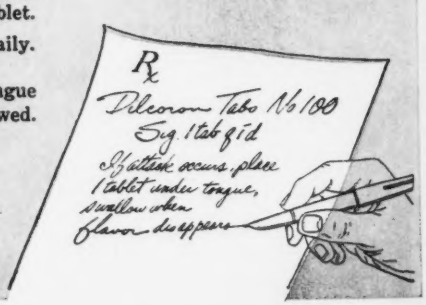

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Editorial

Measurement of Coronary Blood Flow in Man

ATTEMPTS at furthering our knowledge of the regulation of coronary blood flow have, over the past decade, resulted in a distinct shift in methodologic approach. The store of information acquired through the employment of more direct approaches represented by the constant pressure meter for inflow measurement and coronary vein cannulation for outflow quantitation had provided a background for the modern view of coronary vascular physiology.[1] Although the need for a more continuous measurement of flow without disruption of normal aortic pressure was fulfilled by the rotameter, the major advance in overcoming the disadvantages of open-chest anesthetized preparations came with use of the highly diffusible inert gas, nitrous oxide, for cerebral blood flow, later adapted to measurement of left ventricular flow.[2] Potentially this represented a tool for determining left ventricular blood flow in man without distortion of the normal neurohumoral influences upon the heart and its vasculature. Enumeration of current unsolved aspects of coronary function indicate the somewhat limited utility of this method. Nevertheless, it has enabled the accumulation of data in situations paralleling animal work and in circumstances peculiar to man.

Despite the reasonable correspondence of values derived by the gas equilibrium method and simultaneous rotametry, certain theoretic objections have persisted. The assumption of flow homogeneity throughout the heart had been earlier questioned, but has recently been confirmed for the rat heart at least, where perfusion rates of various parts of the left ventricle are substantially the same throughout.[3] Further, the distribution of left coronary artery flow has, except for a small percentage, been established as left ventricular.[4] More importantly for the method's validity, the fraction of myocardial blood draining through the coronary sinus, while not exclusively left ventricular, appears to originate only slightly from elsewhere under a variety of circumstances, so that a disparity between this minor fraction and the left ventricular venous blood would contribute but slight error to this mode of sampling.

Application to hearts in which myocardial fibrosis is present probably does not involve any significant distortion of the blood/tissue partition coefficient for this gas but nonhomogeneity of flow may occur and contribute to failure of blood/tissue equilibration, a situation detectable from the relative arterial-coronary sinus saturations of nitrous oxide.

Although inability to calculate total flow prevents accurate estimation of cardiac external efficiency and the evaluation of certain hemodynamic determinants of myocardial oxygen consumption, sequential assessment in a given patient, permits greater accuracy, and an estimate of the relation of various hemodynamic parameters to myocardial flow and oxygen consumption. Moreover, comparison of sequential values largely averts the unresolved variable represented by the partition coefficient.

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The principal practical disadvantages of the nitrous oxide method for measuring coronary flow are 2-fold. In the first place, one cannot perceive rapid changes in coronary blood flow; reliable data on patients not in a steady state are difficult to obtain. Secondly, although coronary sinus catheterization is not hazardous, it involves careful, time-consuming preparations and some inconvenience to the patient. In addition, intubation of the coronary sinus although feasible in most patients, cannot be accomplished in others due to anatomic variations of the coronary sinus ostium and its surrounding structures.

For this reason, attempts have been made in recent years to overcome these difficulties by introduction of methods in which intubation of the coronary sinus can be avoided and in which rapid variations in coronary flow can be detected. These methods are based either on the uptake of radioisotopes by the heart muscle or on observation and recording of the passage of radioactive tracers through the coronary circulation. The latter method, with the use of the dye-dilution formula of Stewart and Hamilton to calculate the flow, has the advantage of technical simplicity.[5] All that is needed is a device to pick up specific activity of a tracer substance over the precordium and possibly also over a peripheral artery. There is no need for the determination of specific activity in blood. The method, however, suffers from the disadvantage that the peak of precordial radioactivity, which is related to myocardial blood flow, is difficult to differentiate from the other rapid changes in precordial activity such as those resulting from the passage of blood through the right and left sides of the heart. The method is particularly difficult, since the third or coronary peak lies on the extrapolation of the peak in radioactivity, resulting from passage of the radioactive material through the left side of the heart. The method, therefore, awaits further technical improvement to define more sharply the coronary precordial peak in radioactivity. It is not possible to state at the present time whether this will ever become feasible.

Other attempts to measure coronary flow with radioisotopes have tried to utilize the rate of uptake of radioactive material by the heart muscle.[6, 7] Most of these studies have utilized rubidium, Rb^{86}. The element rubidium belongs, like cesium and potassium, in the group-I alkali member series and shows some resemblance to potassium in its physiologic effects. Thus, the heart concentrates rubidium to a degree parallel to that of potassium, although there is a certain predilection of the tissue for rubidium as compared to potassium. Based on this similarity in biologic potassium and rubidium turnover rates, Love and Burch used myocardial uptake of Rb^{86}, as an indicator for coronary blood flow.[7] The authors found that pitressin and *l*-norepinephrine produced changes in Rb^{86} uptake rate that were in the same direction as their known effects on the rate of coronary blood flow. In this laboratory an attempt was made to calculate coronary flow with the Fick principle.[6] Accordingly, the uptake of Rb^{86} by the heart and its coronary arterial-venous difference must be known. If catheterization of the coronary sinus is to be avoided, it must be possible to estimate the concentration of rubidium in coronary vein blood from the myocardial uptake of rubidium and its arterial concentration. The obstacles to accomplish this are considerable. Provided that radiation detection quantitatively determines increments in the myocardial Rb^{86} content, the relationship of myocardial uptake of rubidium and its extraction by the heart to the plasma concentration of rubidium and to the rate of coronary blood flow must be known. It has been shown that the percentage average myocardial Rb^{86} extraction is constant (46 per cent) with respect to arterial rubidium concentration, provided coronary flow remained constant.[6] Experiments on the isolated rabbit heart, however, have clearly shown an exponential relationship not only between the myocardial extraction and the rate of flow, but also between the myocardial extraction and the length of time of perfusion with the isotope. Extraction percentage was significantly lower during the latter portion of the perfusion with a wide

variety of flow rates.[8] This is in agreement with the results of Love and Burch[7] with Rb^{86} and those of Conn and Robertson[9] with K^{42}.

These difficulties are not surprising when one considers the complexities of the kinetics governing the relations of diffusion from the blood stream into the tissues. In the heart, at least, the effective exchange of rubidium between plasma and myocardial interstitial fluid may, like that of potassium, be primarily dependent on or limited by the rate of coronary flow. It is unlikely that in the normally beating heart, double circulation as present in the perfused hind legs, can alter the equilibration curves of rubidium.[10] There is as yet no evidence of a selective perfusion of portions of the coronary circulation in the intact, beating heart. Knowledge of the factors determining the rate of exchange between myocardial, interstitial, and intracellular fluid compartments is at the present still within the stage of speculation.

One is therefore faced with a serious dilemma as to the future efforts that should be made to develop new and more practical methods for determining coronary flow in man. The subject is of such overwhelming clinical and theoretical importance that no avenue of approach should remain unexplored. It is yet possible that despite all difficulties encountered with the use of radioisotopes, these new tools will eventually furnish a workable method for the determination of coronary blood flow in man.

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The Maximal Oxygen Intake Test in Patients with Predominant Mitral Stenosis

A Preoperative and Postoperative Study

By CARLETON B. CHAPMAN, M.D., JERE H. MITCHELL, M.D., BRIAN J. SPROULE, M.D., DAN POLTER, M.D., AND BERNARD WILLIAMS, B.S.

IN FUNCTIONALLY significant mitral stenosis the value of surgical reduction of the block to left atrial outflow is not firmly established. Methods for objective measurement of the degree of functional impairment before and after operation have been slow in development. The critical use of symptoms, physical signs, x-ray films, and electrocardiograms is undoubtedly the first resort for this purpose, and in many cases it is sufficient. In some instances, however, these technics leave important questions unanswered; symptoms do not always fit signs and, most important, subjective improvement after operation is almost the rule even when the usual methods of clinical examination disclose little or no improvement.

Attempts to use quantitative hemodynamic and respiratory methods for evaluation have often been disappointing in that they frequently throw very little light on subjective improvement induced by operation.[1] It may indeed be held that, in the selection of patients for surgery, the superiority of such sophisticated methods over the astute use of ordinary clinical tools has not been demonstrated.

It was inherent in the work by Hickam and Cargill[2] over a decade ago, and in subsequent studies by Gorlin and co-workers,[3] that resting hemodynamic and respiratory studies might be of limited value in the functional evaluation of patients with mitral stenosis unless combined with exercise studies. More recently the effects of exercise on such patients have been studied in detail.[4–6] The strong indication from these studies, and from that by Bruce and colleagues,[7] is that objective measurement, properly applied at rest and during exercise, is a much needed supplement to ordinary clinical evaluation. Most hemodynamic methods, however, are too tedious and cumbersome for routine use in this connection. As a possible substitute, the maximal oxygen intake test is a strong contender since, as recently confirmed in this laboratory,[8] it provides an index to the maximal pumping capacity of the heart. To test its usefulness, maximal oxygen intake, cardiac output, and other items were simultaneously measured in a small group of patients with predominant mitral stenosis, before and after mitral valvulotomy.

Material and Method

The material consisted of 15 men (table 1), all with dominant symptomatic mitral stenosis. According to usual clinical criteria 10 also had some mitral deficiency, and 1 had minimal aortic stenosis. Two had undergone unsuccessful mitral valvular surgery several years previously. Blockage to left atrial outflow was suggested by elevated pulmonary artery wedge pressure (resting) in 9 of the 10 patients who were subjected to cardiac catheterization.

Mitral valvulotomy was done in 10 of the 15 patients but studies before and after operation are available in only 7 of these. Estimates of the size of the valvular opening before and after valvulotomy are given in table 2.

The testing procedure was identical to that previously reported.[8] In brief, maximal oxygen intake was determined on a motor-driven treadmill by use of increasing workloads, each work period lasting 2½ minutes. Much lower treadmill speeds were used than for normal subjects: with the lat-

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Table 1

Clinical Data in Fifteen Patients

Patient no.	Diagnosis	Age	Functional class	Mean pulmonary arterial pressure	Wedge pressure (mm. Hg)	Mean left atrial pressure	Left ventricular pressure
1	MS, MI	39	I	—	—	—	—
2	MS, AS (†)	30	IV	31	20	20	—
3	MS	23	II	25	20	—	—
4	MS, MI	52	III	26	12	15	—
5	MS, MI	33	II	—	—	—	—
6	MS, AS	30	II	23	16	15	103/5
7	MS	30	III	35	21	—	—
8	MS, MI	27	II	18	6	—	—
9	MS, MI	33	IV	21	15	—	—
10	MS	30	III	—	—	—	—
11	MS, MI	39	III	36	19	—	—
12	MS, MI	47	II	23	14	9	85/0
13	MS, MI	30	III	—	—	—	—
14*	MS, MI	35	III	70	34	—	—
15*	MS, MI	31	III	37	—	—	—

*Patients who had been subjected to valvulotomy prior to study and who were being considered for re-operation.

Table 2

Data on Patients Studied before and after Valvulotomy

Patient no.	Height (cm.)	Weight (Kg.)		Surgeon's estimate of mitral valve opening		Body surface area, M.²*	Months between surgery and post-op test
		Pre-op	Post-op	Pre-op	Post-op		
3	174	74.3	78.9	0.8 sq. cm. in area	Admitted 2 fingers	1.88	8.5
4	182	80.5	79.0	Admitted finger tip	Admitted 2 fingers	2.03	3.7
7	168	59.6	64.5	Admitted finger tip	Admitted 3 fingers	1.68	13.3
10	183	64.9	65.0	Would not admit tip of index finger	Admitted 3 fingers	1.85	7.1
11	182	69.6	66.8	1 to 1.5 cm. in diameter	Twice size of original opening	1.90	5.3
13	168	60.1	59.9	About 1.0 cm. in diameter	About 2.0 cm. in diameter	1.68	6.1
14	183	69.4	71.9	7 to 8 mm. in diameter	1 to 1.5 cm. in diameter	1.90	10.9

*Based on preoperative weight.

er, a trot at 6 m.p.h. at grades up to 15 per cent as the usual procedure. In patients with mitral disease, the pace was from 2 to 5 m.p.h., usually t zero grade, depending on the patient's clinical lassification. When the oxygen intake resulting rom a particular workload was not more than 0 ml. greater, or was actually less, than that produced by the previous workload, maximal oxygen ntake was assumed to have been reached. By these ather rigid criteria, 8 of the 15 patients studied preoperatively reached maximal intake. If the criteria be relaxed to conform with those used by other workers,[9] 11 of the 15 patients attained maximal oxygen intake. The other 4 could not accept heavier workloads, and the best that can be said is that they were working at or near capacity. In any event, determination of maximal oxygen intake, while feasible in most patients with mitral disease, is attended by more difficulty than is the case with normal subjects. In the postoperative studies, 5 or 7 patients studied reached maximal intake by the strict criteria. The other 2, having arrived at relatively high intakes, could not perform the next heavier workload. None of the

Table 3

First and Second Trials of Maximal Oxygen Intake Test in Patients with Predominant Mitral Stenosis (Expressed as L./Min.)

Patient no.	First trial	Second trial
1	2.17	2.08
3	2.08	1.98
4	1.77	1.76
6	1.54	1.52
7	1.23	1.31
8	1.40	1.67
9	0.57	0.85
10	1.29	1.26
11	1.34	1.20
13	1.84	2.01
14	1.05	1.22
15	1.00	0.76
Mean	1.44	1.47
S.D.	0.45	0.43

patients developed pulmonary edema although dyspnea was the rule. Monitoring of the electrocardiogram, using a single bipolar lead, permitted early detection of premature ventricular beats or other arrhythmias not present at rest. Upon the appearance of such abnormalities or of severe discomfort, the treadmill was stopped immediately.

Since a "steady state" may be delayed or even unattainable, in patients with mitral disease,[5] the advisability of using such a short work period (2½ minutes) comes into doubt. Practically speaking, the most important question has to do with the ability of the test to characterize a subject, normal or abnormal. Judged in this way, the maximal oxygen intake test appears to provide useful information on patients with mitral stenosis. First and second trials for the test, carried out on 12 of the patients before operation, showed a high order of reliability (table 3). The correlation coefficient (trial 1 versus trial 2) was +0.93. Variance analysis confirms what is obvious from inspection of table 3: most of the variance stems from difference between individuals rather than from differences between trials. After valvulotomy, the result (as judged by repeated tests on 5 patients) becomes even more reliable.

Cardiac output was measured by the dye-dilution method and calculation of "central" blood volume was that devised by Hamilton and coworkers.[10] Samples of arterial and venous (femoral and brachial) blood were collected by means of inlying catheters. Standard analytical methods were used throughout except that arterial and venous pO_2 was determined polarographically.[11] The experimental design was such that all determinations were made at rest, with the patient standing, and during (not after) exercise.

Results

Respiratory Items

Resting oxygen intake (patient standing) was virtually identical with that previously observed in normal men[8] (table 4). Operation did not significantly affect resting oxygen intake when measured 3.7 to 13.3 months after surgery. Wade and co-workers,[4] found that resting oxygen intake had declined somewhat in most patients 2 years after mitral valvulotomy. They also found that before operation, patients with mitral stenosis show increased resting oxygen intake (as compared with normal) and attributed the finding to increased work of breathing. The present results are not in agreement, possibly owing to differences in case material and in experimental plan.

Maximal oxygen intake (table 5) was markedly restricted in unoperated patients. The mean value in the patients (1.43 ± 0.45 L./min. for the entire group, and 1.54 ± 0.34 L./min. for patients studied before and after operation) is to be compared with the value 3.22 ± 0.46 L./min. obtained in 15 normal men.[8*] Age being taken into account and maximal oxygen intake being expressed as ml./Kg./min., comparable values are 21.6 ± 6.1 for patients and 39.3 ± 3.9 for normal subjects. The values were not significantly altered by excluding those patients who may not have reached maximal oxygen intake as judged by the criteria developed for normal subjects. Valvulotomy was associated with increase in maximal oxygen intake in all 7 patients who were studied before and after surgery. The difference between the means (1.54 and 1.82 L./min.) was not significant, but the directional change in all 7 patients cannot be discounted. Although all patients were improved, none was able to attain the normal average value after surgery.

Pulmonary ventilation (table 4) at rest was not significantly affected by valvulotomy; at maximal oxygen intake, pulmonary ventilation before surgery was considerably lower than the previously observed normal value (62.2 ± 11.0 L./min. in patients and 89.4 ± 17.3

*The same results, expressed as ml./Kg./min., are 21.8 ± 5.9, 22.1 ± 4.6, and 44.6 ± 5.0, respectively.

Table 4

Respiratory Factors in Patients before and after Valvulotomy

Patient no.	Oxygen intake, L./min., STPD*				Pulmonary ventilation, L./min., BTPS†				Oxygen removal rate			
	Pre-op.		Post-op.		Pre-op.		Post-op.		Pre-op.		Post-op.	
	Rest	Max.	Rest	Max.	Rest	Max.	Rest	Max.	Rest	Max.	Rest	Max.
3	—	2.08	0.34	2.13	—	80.55	10.34	97.60	—	25.8	32.9	20.8
4	0.38	1.89	0.46	1.93	14.38	67.59	16.36	72.75	25.6	28.0	28.1	26.5
7	0.27	1.31	0.33	2.11	10.20	41.87	11.04	71.28	26.5	31.3	29.9	29.6
10	0.38	1.29	0.32	1.78	15.01	57.39	10.36	49.11	25.3	22.5	30.9	36.2
11	0.32	1.34	0.31	1.63	13.39	63.99	11.21	81.60	23.9	20.9	27.7	20.0
13	0.34	1.84	0.33	1.89	12.61	66.49	12.85	83.03	27.0	27.7	25.7	22.8
14	—	1.05	0.34	1.26	—	57.52	10.24	52.58	—	18.3	33.2	24.0
Mean	0.34	1.34	0.35	1.82	13.4	62.20	11.77	72.56	25.7	24.9	29.8	25.7
S.D.	0.04	0.36	0.15	0.24	1.75	10.99	2.05	15.90	1.1	4.2	2.6	5.3

*Standard temperature pressure dry.

†Body temperature pressure saturated.

L./min. in corresponding normal subjects). Surgery produced an increase in pulmonary ventilation in 5 of the 7 subjects. Valvulotomy appeared to cause a slight increase in *rate of oxygen removal* at rest; during heavy exercise, little change was seen in the values as compared to the resting ones, either before or after operation. It was previously observed in normal subjects that progressive increase in workloads up to that producing maximal oxygen intake is associated with a progressive decline in oxygen removal rate. In patients with mitral stenosis, an insignificant decline between the resting value and that at the maximal intake load was seen. The differences observed, however, are too small to justify the acceptance of the finding as a means of differentiating patients from normal subjects.

Circulatory Factors

Resting *cardiac output* was slightly lower in the patients than in comparable normal men and was unaltered by valvulotomy (table 6). Resting *pulse rate* and *stroke volume* were in the normal range before and after surgery. Resting *arteriovenous oxygen difference* was slightly (but not significantly) higher than the normal value previously reported (6.5 ± 0.7 vol./100 ml.) and was also unaffected by surgery. *Appearance and mean circulation times* at rest were slightly prolonged in the patients and, like the other items in table 6, were not significantly altered by surgery.

Exercise, at or near the level producing maximal oxygen intake, caused a 2-fold increase in cardiac output before surgery and very nearly a 3-fold increase after surgery (table 7). Before surgery, the increase in cardiac output was accomplished entirely by elevation in pulse rate; after surgery, augmentation of stroke volume made a significant contribution to the increase in cardiac output produced by heavy exercise. Surgery also produced a significant alteration in mean circulation and appearance times (at the maximal intake level) toward normal. The arteriovenous oxygen difference was markedly increased by exercise before surgery (17.8 ± 3.4 compared to 14.3 ± 2.5 ml./100 ml. in normal subjects) and was only slightly above normal after operation (15.3 ± 2.6 ml./100 ml.).

As for the distribution of blood volume in the patients studied, the only data available are those derived from the dye-dilution studies (cardiac output × mean circulation time), which are thought to provide an index to some aspect of *central blood volume*: the amount of blood present in the system from the point of injection to the point of arterial sampling. While it may safely be assumed that the volume of blood in the exercising muscles was greater than that present in the same muscles at rest, no attempt at measurement of the increment was made.

Under resting conditions the injection-to-

Table 5

Maximal Oxygen Intake in Entire Group of Patients and in Comparable Normal Subjects

Patient no.	Expected		Preoperative		Postoperative	
	Total, L./min.	ml./Kg./min.	Total, L./min.	ml./Kg./min.	Total, L./min.	ml./Kg./min.
1	3.04	39.3	2.17	33.7	—	—
2	3.04	39.3	.78	13.6	—	—
3	3.37	44.7	2.08	27.0	2.13	31.3
4	2.46	32.0	1.89	23.8	1.93	24.2
5	3.04	39.3	1.92	23.7	—	—
6	3.04	39.3	1.54	25.2	—	—
7	3.04	39.3	1.31	22.1	2.11	32.7
8	3.37	44.7	1.40	22.7	—	—
9	3.04	39.3	.57	11.6	—	—
10	3.04	39.3	1.29	19.8	1.78	26.1
11	3.04	39.3	1.34	19.1	1.63	24.3
12	2.94	35.4	1.33	23.9	—	—
13	3.04	39.3	1.84	29.7	1.89	31.7
14	3.04	39.3	1.05	15.0	1.26	17.3
15	3.04	39.3	1.00	16.6	—	—
Mean	3.03	39.3	1.43	21.8	1.82	26.8
S.D.	.21	2.9	0.45	5.9	0.24	5.1

sampling volume of blood was virtually the same in patients with mitral stenosis as that previously found in normal subjects (table 6). In such patients, however, the volume was higher, relative to resting cardiac output, than in normal subjects. In the group of patients, the ratio injection-to-sampling volume: cardiac output was 0.39; in normal subjects it was 0.32. With exercise, the injection-to-sampling volume rises, as does cardiac output, in normal subjects and in patients with mitral stenosis (table 7). The line relating the 2 variables, in which x = cardiac output and y = injection-to-sampling volume, is steeper in patients with mitral stenosis than in normal subjects. For the latter (16 subjects, 59 measurements) the regression equation was

$$y = 1.191 + 0.092x$$

and the correlation coefficient was 0.87. For patients with mitral stenosis, the corresponding equation was

$$y = 1.460 + 0.137x$$

and the correlation coefficient was 0.59. The same correlation coefficient and virtually the same regression equation were obtained with the postoperative data.

Blood Gas Studies

At rest, the patients with mitral stenosis, did not appear to differ appreciably from normal subjects with regard to gas constituents and pH of arterial and venous blood except that the patients showed a small degree of arterial oxygen desaturation (table 8). The changes produced by exercise were qualitatively similar to those seen in normal subjects. The slight degree of arterial oxygen desaturation was somewhat lessened by exercise, both before and after operation. Arterial oxygen tension at rest was normal and rose slightly during exercise before operation. After surgery, arterial oxygen tension was lower than before but was well maintained during exercise. Venous oxygen tensions, as well as can be judged from the small number of samples that could be collected, were lower at rest than normal and were less well maintained during exercise.

Arterial pH, which was normal at rest, fell less during exercise than in normal subjects. Changes in venous pH in the patients were similar to those seen in normal subjects. At the same time, arterial carbon dioxide tension, normal at rest, fell slightly during exercise.

Discussion

The maximal oxygen intake test appears to provide an objective but approximate guide to the degree of functional disability in patients with predominant mitral stenosis. The data are not extensive enough to permit detailed correlation with other objective measurements such as cardiac output, left atrial mean pressure, and pulmonary arterial pressures, mean or wedged. Although the highest pressures tended to be associated with low values for maximal oxygen intake (in terms of per cent of expected normal), several exceptions were present. The same comment can be made with regard to cardiac output at maximal oxygen intake. In terms of clinical classification, it can be seen that of 10 patients who were in classes III or IV, 8 showed markedly depressed maximal oxygen intakes

Table 6

ge-Dilution Data in Resting Men with Predominant Mitral Stenosis before and after itral Valvulotomy

	Preoperative							Postoperative						
Patient no.	Cardiac output, L./min.	Pulse rate (min.)	Mean stroke vol., ml.	AVO_2 diff., ml./100 ml.	Central blood vol., liters	Mean circ. time, sec.	Appearance time, sec.	Cardiac output, L./min.	Pulse rate (min.)	Mean stroke vol., ml.	AVO_2 diff., ml./100 ml.	Central blood vol., liters	Mean circ. time, sec.	Appearance time, sec.
3	5.5	95	58	—	2.24	24	14	6.8	89	76	5.4	2.29	20	12
4	—	88	—	—	—	—	—	4.4	90	49	10.3	2.20	30	16
7	4.0	90	44	6.8	1.11	17	10	5.8	88	66	5.7	1.34	14	8
10	5.5	90	61	6.9	1.99	22	14	3.6	105	34	8.9	1.02	17	8
11	3.7	88	42	8.6	2.25	37	18	3.7	—	—	8.4	1.54	25	16
13	5.0	64	78	6.8	1.61	19	12	5.1	75	68	6.3	1.28	15	6
14	—	82	—	—	—	—	—	4.1	70	59	8.3	2.10	31	18
Mean	4.7	85	57	7.3	1.84	24	14	4.8	86	59	7.6	1.68	22	12
S.D.	0.8	9	13	0.8	0.43	7	3	1.1	11	14	1.7	0.47	7	4

(less than 60 per cent of expected). All 5 of the patients in class I or II came nearer to a normal value.

The test was helpful in evaluating patients in several instances. In case 1, a prominent rumbling diastolic murmur was present but the patient presented few symptoms attributable to mitral stenosis itself. The maximal oxygen intake test, as we interpret it, showed that very little blockage to left atrial outflow was present and thus confirmed the clinical evaluation. In case 12, a severe cardiac neurosis and self-imposed physical inactivity made clinical classification difficult. The maximal oxygen intake test confirmed the presence of moderate valvular stenosis but was not in keeping with tight stenosis. For this reason, and because the patient could not be persuaded to alter his very sedentary ways, valvular surgery was withheld. In case 5, maximal oxygen intake was about 60 per cent of expected, although the patient was hard at work and denied severe symptoms. Because of the discrepancy, surgery was not recommended at the time. Two years later, however, the patient was almost completely disabled and valvulotomy was carried out with excellent results. Unfortunately, postoperative studies could not be done to verify the clinical impression of marked improvement. The test did, however, reflect striking clinical improvement in cases 7, 10, and 14.

The maximal oxygen intake test seems, therefore, to provide a legitimate and objective means of evaluating the degree of blockage to left atrial outflow when clinical methods are for any reason inadequate. Its chief advantage is that it characterizes performance under stress in a physiologically meaningful way, at or near capacity levels, and does not require right or left cardiac catheterization. Its chief disadvantage is that some patients cannot or will not finish the test. Another disadvantage at the present time is that it cannot be used with female patients owing to the absence of adequate normal data for the female sex. Taken as a whole, the data are in accord with previous views that in patients with mitral stenosis, response to exercise is characterized by marked limitation of increase in cardiac output and in maximal oxygen intake; inability to increase stroke volume; marked widening of arteriovenous oxygen difference; and probable increase in some aspect of central blood volume over that seen in normal subjects.

The genesis of the inability of patients with predominant mitral stenosis to increase cardiac output in response to exercise is of some interest. It is obvious that there is no unusual

Table 7

Dye-Dilution Data at Maximal Oxygen Intake in Men with Predominant Mitral Stenosis before and after Mitral Valvulotomy

	Preoperative							Postoperative						
Patient no.	Cardiac output, L./min.	Pulse rate, (min.)	Mean stroke vol., ml.	AVO_2 diff., ml./100 ml.	Central blood vol., liters	Mean circ. time, sec.	Appearance time, sec.	Cardiac output, L./min.	Pulse rate, (min.)	Mean stroke vol., ml.	AVO_2 diff., ml./100 ml.	Central blood vol., liters	Mean circ. time, sec.	Appearance time, sec.
3	14.8	187	79	13.4	3.48	14	10	16.5	191	86	15.3	3.91	14	10
4	9.6	167	57	18.3	4.58	29	16	9.8	—	—	19.0	3.48	21	14
7	6.7	169	40	20.6	1.65	15	8	12.5	178	70	16.9	2.00	10	6
10	8.2	185	44	15.4	3.25	24	16	12.9	181	71	13.8	2.62	12	6
11	5.1	144	35	23.5	2.44	29	16	8.6	—	—	17.7	3.74	26	16
13	12.8	178	72	15.7	3.03	14	10	17.3	165	105	11.0	3.46	12	8
14	—	163	—	—	—	—	—	11.8	177	67	13.6	4.92	25	16
Mean	9.5	170	55	17.8	3.07	21	13	12.8	178	80	15.3	3.45	17	11
S.D.	3.4	14	16	3.4	0.90	7	3	3.0	8	14	2.6	0.87	6	5

limitation in the ability of such a patient to increase pulse rate. Stroke volume, however, can be increased very little or not at all. The role of change in pulse rate versus that in stroke volume in adaptation of the normal human subject to exercise has recently been somewhat revised by Rushmer.[12, 13] His data suggest that augmentation of stroke volume is less significant than increase in pulse rate in this connection. He makes allowance, however, for the possibility that increase in stroke volume may be called into play under rather exceptional circumstances, such as very heavy exercise. It seems to the present authors that Rushmer's vigorous rejection of older physiologic "dogmas" is too sweeping. It has been clearly shown in this laboratory that stroke volume in normal subjects at exercise loads producing maximal oxygen intake is about twice as great as that prevailing during resting conditions (subject standing). The behavior of stroke volume during exercise loads of intermediate severity is currently under scrutiny. It may be that stroke volume changes very little, after an initial increase with change from the standing resting state to low-level exercise, until very heavy loads are reached; but the point is not yet settled. Be this as it may, the normal subject *does* utilize increase in stroke volume, as well as in pulse rate, in adapting to heavy exercise under conditions that can only be regarded as physiologic. It is also clear that the normal mechanism is modified in patients with mitral stenosis. In them, but not in normal subjects, augmentation of stroke volume seems to behave more nearly in accord with Rushmer's concept. Valvulotomy not only permits greater increase in cardiac output with exercise but also permits the increase to be achieved in a manner qualitatively similar to that regularly seen in normal subjects.

Extreme widening of the arteriovenous oxygen difference during exercise in patients with mitral stenosis may be regarded as an exaggeration of one of the normal mechanisms for ensuring adequate oxygenation of active muscle cells. The pertinent question is, "can the patient with mitral stenosis working at the maximal oxygen intake level extract relatively more oxygen from blood perfusing active muscle than the normal subject under similar conditions?" It was shown earlier[14] that, in the normal subject, femoral venous oxygen tension is relatively well maintained although corresponding oxygen saturation may fall to very low values, during heavy treadmill exercise. It has been suggested, but not proved, that venous oxygen tension may approach zero during relatively heavy exercise in patients with severe cardiac disease.[5] In the present study the number of measurements of

Table 8

Mean Values for Various Blood Constituents in Patients with Predominant Mitral Stenosis before and after Valvulotomy, at Rest (R) and at Maximal Oxygen Intake (M)

		O_2 content ml./100 ml.	O_2 tension mm. Hg	Per cent sat.	pH	Plasma CO_2 content ml./100 ml.	CO_2 tension mm. Hg
Preoperative							
Brachial Artery	R (N*=6)	16.1±1.7	83±11	92.1±4.6	7.40±.06	23.8±1.0	37±6
	M (N =6)	17.4±1.9	91±25	93.8±8.0	7.30±.09	17.4±2.0	34±6
Brachial Vein	R (N =2)	9.4	29	53.8	7.43	26.1	38
	M (N =1)	2.5	13	13.3	7.21	28.1	66
Femoral Vein	R (N =2)	10.1	19	57.9	7.37	28.2	47
	M (N =2)	3.0	16	15.4	7.18	28.9	62
Postoperative							
Brachial Artery	R (N =7)	17.3±2.1	75±16	93.4±5.4	7.43±.04	24.9±1.5	36±3
	M (N =7)	18.2±1.2	73±17	94.8±4.1	7.33±.07	15.9±4.0	28±7
Brachial Vein	R (N =6)	9.2±3.2	30±8	49.3±16.1	7.38±.07	27.8±3.3	43±8
	M (N =3)	2.7±1.3	22±11	13.4±6.2	7.14±.07	27.5	80
Femoral Vein	R (N =7)	5.6±2.0	20±5	30.1±10.0	7.38±.06	28.3±2.5	47±6
	M (N =7)	2.5±2.1	17±7	12.6±10.1	7.15±.06	26.3±2.8	73±12

*Number of patients.

femoral venous pO_2 before operation (2 patients) is too small to permit generalization but the data do not bear out the suggestion that the value approaches zero during exercise in such patients (table 8). Such a phenomenon would probably result in a negative pO_2 gradient between the venous capillaries of exercising muscle and the muscle cell itself. Such a reversal, if it should occur, could hardly prevail for more than an extremely short period of time. It is quite possible that the nature of the oxygen dissociation curve of myoglobin confers a unique ability to withstand low oxygen tensions on voluntary muscle cells. Since the curve is parabolic, rather than S-shaped, the per cent saturation of myoglobin can be relatively well maintained in spite of very low oxygen tension in the cell itself. Thus, a positive oxygen tension gradient from capillary to cell might be maintained at capillary oxygen tensions of a few mm. Hg. This possibility, however, is probably not limited to patients with cardiac disease, and may conceivably be a factor in normal subjects undergoing violent exercise near the point of exhaustion. In any case, the extent to which venous and myocellular oxygen tensions are limiting factors in heavy exercise has yet to be fully elucidated.

The small degree of arterial oxygen desaturation in patients with mitral stenosis has no ready explanation. It may be attributable to certain pulmonary factors but no attempt was made in the present study to identify them.

The data on "central" (injection-to-sampling) blood volume are in agreement with the report by Rapaport and colleagues[15] in that the resting value is larger in patients with mitral stenosis, relative to cardiac output, than in normal subjects. In the patients, as in normal subjects, exercise produces an increase in cardiac output and in injection-to-sampling volume but in the former, the rise is greater, relative to cardiac output, than in the latter. It has recently been suggested that the increase in injection-to-sampling volume during exercise may be an artifact, when the brachial artery is used as the sampling site, attributable to decrease in blood flow to the inactive extremity.[16] While such a decrease in flow is well documented, convincing evidence is lacking that the observed increase in injection-to-sampling volume in exercising human subjects is more apparent than real. Recent work by Braunwald and co-workers,[17] in which the arm used as a sampling site was heated in order to minimize decrease in blood flow, still showed an increase in injection-to-sampling

volume during exercise. It seems premature, therefore, to reject the observed increase in injection-to-sampling volume associated with exercise as a technical artifact. The physiologic meaning of such an increase, if it occurs, is not yet known. The difference in behavior of the injection-to-sampling volume during exercise between patients with predominant mitral stenosis and normal subjects may be due to an increase in left atrial volume (in the patients) as flow increases but the matter cannot be regarded as settled.

Finally, the results show that valvulotomy induces change toward normal in most of the variables studied, although the degree of change is usually small. It would obviously be unreasonable, however, to conclude that the changes are functionally insignificant. In actual fact, some of the changes seen as a result of valvulotomy were rather impressive; arteriovenous oxygen difference (at maximal oxygen intake) was restored nearly to normal and the ability to increase stroke volume was definitely increased. It is also quite likely that the interval of time between valvulotomy and postoperative studies was so short, in some instances, that less-than-maximal benefits were observed. The operation, in any case, is capable of reducing the degree of abnormality induced by stenosis of the mitral orifice and the effect of the procedure can be gaged by comparison of maximal oxygen intake before and after surgery. While the discrepancy between quantitative improvement in physiologic variables and in symptomatic improvement is still not satisfactorily explained, it may well be that a small degree of improvement in the patient's ability to respond to stress can produce marked amelioration of symptoms.

Conclusions

The maximal oxygen intake test can be used as an objective means of evaluating the degree of dynamic impairment in many patients with mitral stenosis.

The response of patients with mitral stenosis to exercise differs from that of the normal subject in that ability to increase stroke volume is limited; widening of arteriovenous oxygen difference is more marked and oxygen tension of blood returning from active muscle is lower; and "central" blood volume is increased relatively more, at any given level of cardiac output, as exercise loads rise.

Mitral valvulotomy in patients with mitral stenosis causes a definite change toward normal of the dynamic response to exercise.

Summario in Interlingua

Le test del ingresso maximal de oxygeno pote sser usate como medio objective pro evalutar le grado del disturbation dynamic in multe patientes con stenosis mitral.

Le responsa de patientes con stenosis mitral al effortio de un exercitio differe ab illo del subjecto normal in tanto que lor capacitate de augmentar le volumine per pulso es restringite. Le intensification del differentia arterio-venose de oxygeno es plus marcate, e le tension oxygenic del sanguine que retorna ab musculos active es plus basse. Le augmento del volumine de sanguine "central" es relativemente plus marcate a omne nivello particular de rendimento cardiac durante que le carga del exercitio es augmentate.

Valvulotomia mitral in patientes con stenosis mitral causa definitemente un alteration verso le stato normal in le responsa dynamic a exercitios.

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Vesalius

In 1537, after a year's stay at Louvain where, in the February of that year, Vesalius at the age of 22 put forth his first juvenile effort, a translation of the ninth book of Rhazes, he migrated to Venice, the enlightened if despotic government of which was in all possible ways fostering the arts and sciences, and striving to develope in the dependent city of Padua a University which should worthily push on the new learning. . . .

The brilliant talents of the young Belgian at once attracted the notice of the far-sighted rulers of Venice. He was in December of that same year, 1537, made Doctor of Medicine in their University of Padua, was immediately entrusted with the duty of conducting public dissections, and either then or very shortly afterwards, though he was but a lad of some one or two and twenty summers, was placed in a chair of Surgery with care of Anatomy. . . .

Five years he spent in untiring labours at Padua. Five years he wrought, not weaving a web of fancied thought, but patiently disentangling the pattern of the texture of the human body, trusting to the words of no master, admitting nothing but that which he himself had seen; and at the end of the five years, in 1542, while he was as yet not 28 years of age, he was able to write the dedication to Charles V. of a folio work, entitled the 'Structure of the Human Body,' adorned with many plates and woodcuts, which appeared at Basel in the following year, 1543. . . .

This book is the beginning not only of modern anatomy but of modern physiology.—SIR M. FOSTER. *Lectures on the History of Physiology.* London, Cambridge University Press, 1901.

Interarterial Coronary Anastomoses and Coronary Arterial Pattern

A Comparative Study of South African Bantu and European Hearts

By W. J. Pepler, D.Sc., M.D., and B. J. Meyer, D.Sc., M.B., Ch.B.

THE QUESTION whether intercoronary anastomoses exist in normal and pathologic human hearts has been the subject of vigorous discussion for many decades. Apart from the purely scientific interest the problem may have, it is of the greatest clinical importance for the better evaluation of the problems and possible future treatment of angina pectoris and acute myocardial infarction. Furthermore, familial or racial differences in the degree of anastomoses might to some extent be responsible for the varying frequency of myocardial infarction among different races and also among different families in the susceptible races. The important practical aspects of the problem have been clearly summarized by Blumgart et al.,[1] who stated "anastomotic circulation to an extraordinary degree may obviate any serious consequences of complete coronary artery occlusion."

Many of the controversial results concerning the presence or absence of significant intercoronary arteriolar anastomoses can certainly be ascribed to differences in the technics employed by the various investigators. This fact was pointed out by Laurie and Woods,[2] but subsequently their technic has again been criticized by Blumgart and Zoll.[3] In applying their modified Schlesinger technic to Bantu hearts only, Laurie and Woods[2] obtained results so different from the American workers who have actually originated and standardized the technic that the entire question now needs critical reassessment. Although it has been pointed out to Laurie and Woods that their results might be due to racial or environmental factors,[3–5] they have subsequently reaffirmed their statements[6, 7] of the existence in all races of functionally important anastomoses in the majority of healthy people over the age of 4 years, thus supporting Baroldi, Mantero, and Scomazzoni's[8] claim that anastomoses are almost the rule in normal hearts.

In yet another article, Laurie and Woods[9] made the controversial statement that the serious effects of atherosclerosis are seen in the Bantu hearts (coronary artery disease) and that they do not "enjoy any relative freedom from atherosclerosis." This remark has already been quoted as implying that the Bantu do develop coronary thrombosis fairly commonly.[10] From these statements one may infer that the existence of anastomoses do not offer any relevant safeguard against the development of myocardial infarction. Yet it has been conclusively shown by other workers in South Africa that, although the incidence of coronary and aortic atheroma appears to be the same, the severer degrees of the disease appear to be less among the Bantu.[11, 12] The rarity of cardiac infarction in the Bantu has been confirmed by Schrire and Uys.[13] In 1958 Becker[14] again stressed that the incidence of the serious complications of atherosclerosis, such as coronary occlusive disease, is much lower in the Bantu than in the European but "that on occasion the Bantu can and does develop just as much atherosclerosis as the European. . . ." In the absence of complications, this in itself would seem to implicate local vascular factors in the very low incidence of myocardial infarction in the Bantu. This hypothesis is further strengthened by the observations of Laurie and Woods[9] and of

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Walker and Simson,[15] who reported a relatively high rate of cerebrovascular accidents in the same race.

That local anatomic variations must be considered in explaining the difference between Bantu and European hearts has been suggested in a preliminary study by Brink.[16] The validity of his findings have, however, since then been questioned by Singer,[17] who investigated a much larger group of subjects. Brink[16] also suggested that the anatomic variations might be responsible for the lower incidence of angina pectoris and coronary thrombosis. This conclusion has also been questioned by Elliot.[18]

In view of these controversial reports, it seemed advisable to investigate the question of coronary anastomoses and coronary arterial patterns in a group of European and Bantu autopsies, with the use of the same technic in both groups. The present paper reports our findings on a series of 188 Bantu and European hearts.

Material and Methods

Material

Of the 188 cases in the present study, 167 were in-patients dying in the Pretoria General Hospital, an institution with 913 European and 665 non-European beds. The remaining 21 hearts were obtained from the Government Medico-Legal Laboratories; these cases died from unnatural causes but were otherwise free from any detectable disease. Of the 21 cases, 11 were European children and adolescents and were all included in the age groups 0 to 9 and 10 to 19 years. The remaining 10 cases were old Bantu and were included in order to fill the age groups 70+ years. The age and sex incidence of the 2 racial groups is given in table 1.

Postmortem examinations are obtained on approximately 17 per cent of the patients dying in this hospital. The main reason for the low percentage of cases on whom autopsies are performed is failure to obtain permission from relatives. The cases obtained from the hospital had all died from natural causes and the series was entirely unselected, except for age. As soon as 10 to 12 cases had been investigated in a specific age group, the collection of further cases in the group in question was stopped. The cases included in the series died from a wide range of pathologic conditions. All the postmortem examinations were under our supervision.

Table 1

Age and Sex Distribution of the Series

Age group (years)	European		Bantu	
	Male	Female	Male	Female
0 — 9	2	4	2	8
10 — 19	7	3	4	8
20 — 29	7	3	6	4
30 — 39	5	6	6	5
40 — 49	5	5	9	5
50 — 59	5	5	5	6
60 — 69	4	6	6	6
70 — 79	8	4	7	3
80 — 89	7	4	4	4
Total	50	40	49	49

Methods

The hearts were immediately injected after removal from the body according to the latest modification of the Schlesinger technic,[19] in which a gelatin-potassium-iodide-barium sulfate mixture is employed. This mixture can be solidified at room temperature by adding varying concentrations of formalin prior to injection of the mass. The "viscosity conversion concentration" of every freshly prepared batch was determined, and the amount and concentration of formalin added were regulated so that solidification of the mass took place in approximately 30 minutes. Our technic conformed entirely to that of Schlesinger except that after injection of saline into both coronary ostia, the radiopaque mass was injected into the left coronary artery only for a period of exactly 3 minutes. The mass was injected at a pressure corresponding to the mean arterial blood pressure of the individual if this was known, and in all other cases at a pressure of 100 mm. Hg. During this period the hearts were closely scrutinized for any evidence of intercoronary anastomoses. The anastomoses were recorded as "good" in those cases in which the right coronary arterial tree was completely filled by the mass injected into the left coronary orifice within the specified 3 minutes. Anastomoses were recorded as "moderate" when the right coronary tree was not filled but when clear-cut evidence of an admixture of the different colors injected in the 2 trees could be demonstrated in the right coronary system on dissection of the fixed specimen. The same system was used to determine the absence of anastomoses.

Subsequently the right coronary arterial tree was injected under the same pressure. At the same time the pressure was maintained in the left coronary circulation. As soon as the injection mass stopped flowing, the cannulas were clamped and the heart was suspended in 10 per cent neutral formalin for 1 to 2 hours. The hearts were then dissected ac-

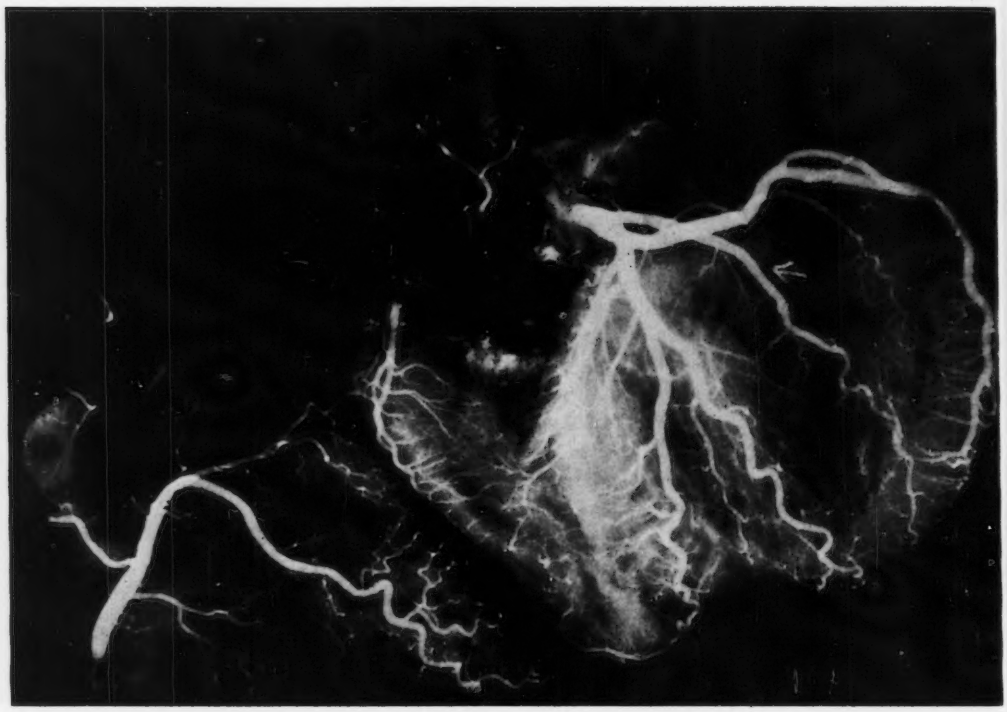

Figure 1

Roentgenogram of the heart of a 45-year-old Bantu man with a third primary division of the left coronary artery.

cording to the modification of Rodriguez and Reiner.[20] The "unrolled" hearts were fixed in neutral 10 per cent formalin for a few more days and then photographed by x-ray. Subsequently 8 blocks were taken from each heart for microscopic examination and at the same time the coronary tree was dissected and the degrees of luminal narrowing were recorded.

Four of the Bantu hearts were omitted in our assessment of the degree of anastomosis because of a faulty injection technic.

All statistical analyses were done according to the chi-square test method.

"Third Primary Division of the Left Coronary Artery"

Although the term "third primary division of the left coronary artery" was originated by Brink[16] 10 years ago, not until recently was the coronary artery pattern in the Bantu reinvestigated by Singer.[17] The publication of this article was followed by a series of letters by both authors[21, 22] in which each other's methods, terminology, and interpretations were variously criticized. Unfortunately the significance of any racial anatomic variation in collateral or anastomotic circulation was ignored. Brink[16] tentatively proposed that the third primary division of the left coronary artery, which he has regarded as an extra branch of the left coronary artery, could be an important source of collateral circulation. He suggested that his findings may explain the rarity of myocardial infarction and angina pectoris in the Bantu.

In the present series it was necessary to re-evaluate these findings in an attempt to correlate the presence or absence of a third primary division of the left coronary artery with the anastomoses demonstrated with the present technic.

The x-ray films were labeled in such a way that it was not possible to identify the racial

Figure 2

Roentgenogram of the heart of a 19-year-old European man with a small third primary division of the left coronary artery.

group of the case. These films were then interpreted independently by both authors as to the presence or absence of a third primary left ventricular artery. The presence of such an artery was accepted only if both branches 12 and 14 of Spalteholz[23] (the nomenclature used by Brink[16]), or as Singer[22] has renamed them, the major and minor left ventricular arteries, were clearly present. Furthermore, the third branch had to originate in the angle formed by the primary branches (figs. 1 to 4). In any case in which it was not possible because of overlapping on the x-ray film to determine the exact origin of the artery in question, the heart was dissected. This was done in 40 per cent of the cases in the series.

At the same time, the distribution of the coronary arteries was also noted, i.e., whether the heart belonged to the right preponderant, left preponderant, or balanced type of circulation.[24] In this regard no significant differences were observed in the 2 groups.

By the use of the described technics, the presence of a third primary division of the left coronary artery was demonstrated in 38 per cent of European hearts (table 2). In the Bantu, on the other hand, this artery was present in 74 per cent. Therefore our findings confirm those of Brink[16] in that the presence of the third primary division of the left coronary artery is significantly higher in the Bantu than in the European group. The probability that there is no difference in this respect is extremely low ($p = <0.01$). No correlation could, however, be established between the presence or absence of this artery and the presence or absence of a functionally important anastomotic circulation between the left and right coronary arterial system. That it may facilitate the anastomotic circulation of the left coronary tree could not be excluded.

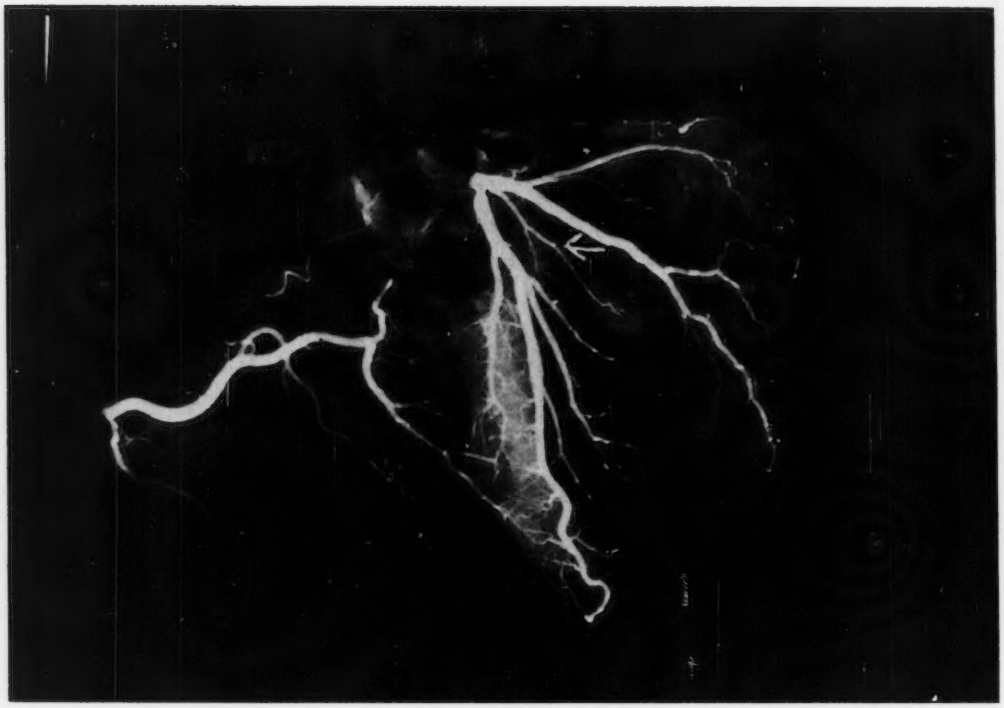

Figure 3

Roentgenogram of the heart of a boy aged 17 in which the third primary division is a replacement of branch 14 of the Spalteholz classification.

Table 2

Incidence of Third Primary Division of the Left Coronary Artery

Age group	European			Bantu		
	Number of cases	3rd P.* present	3rd P. absent	Number of cases	3rd P. present	3rd P. absent
0 — 9	6	1	5	10	8	2
10 — 19	10	5	5	12	8	4
20 — 29	10	4	6	10	6	4
30 — 39	11	4	7	11	10	4
40 — 49	10	7	3	14	10	1
50 — 59	10	6	4	11	9	4
60 — 69	10	3	7	12	8	2
70 — 79	12	3	9	10	7	3
80 — 89	11	1	10	8	6	2
Total	90	34	56	98	72	26

*Third primary division of the left coronary artery.
$\chi^2 = 24.3$; degree of freedom $= 1$; $p = <0.01$.

Intercoronary Arteriolar Anastomoses

The age and sex distribution of the cases with "good," "moderate," and "no" demonstrable interarterial coronary anastomoses are depicted in table 3. This analysis includes all cases of the 2 racial groups irrespective of associated pathologic changes. In the Bantu series we confirmed the findings of Laurie and Woods[2] that functionally important anastomoses do exist in a high percentage of cases: "good" anastomoses were demonstrated in 54 of 94 hearts, i.e., in 57 per cent. In the European group, on the other hand, only 23 of 90 cases (26 per cent) showed anastomoses of a comparable degree. This difference is highly significant statistically as measured by the chi-square test or standard error of difference. Separate analysis of the age groups above and below 20 years shows the same significant statistical difference. This result clearly indi-

Figure 4

Roentgenogram of the heart of a Bantu woman aged 80 with very severe coronary atherosclerosis and narrowing of the lumen. On dissection a third primary division of the left coronary artery was demonstrated.

cates that the findings of Laurie and Woods[2] cannot be applied to all ethnic groups as they have done. On examination of the age distribution of the cases with functionally important anastomoses it becomes apparent that, whatever the cause of the development of the anastomoses, it must be present at a very early age because 7 of the 10 Bantu cases in the age group 0 to 9 years had excellent anastomotic circulation. It was then decided to reclassify the cases into groups with normal hearts, hypertrophied hearts, and hearts with severe coronary atherosclerosis in order to assess the various factors that may be involved in the development of interarterial coronary anastomoses.

Normal Hearts and Coronary Anastomoses

The hearts included in this group showed no macroscopic or microscopic evidence of peri-

Table 3

Degree of Intercoronary Anastomoses in Both Racial Groups

	European				Bantu			
		Anastomosis				Anastomosis		
Age group	No. cases	Good	Moderate	Nil	No. cases	Good	Moderate	Nil
0 — 9	6	2	1	3	10	7	1	2
10 — 19	10	2	3	5	10	10	–	–
20 — 29	10	4	4	2	10	5	3	2
30 — 39	11	2	4	5	11	6	3	2
40 — 49	10	3	2	5	14	9	4	1
50 — 59	10	2	2	6	11	6	1	4
60 — 69	10	2	4	4	10	3	3	4
70 — 79	12	3	2	7	10	6	2	2
80 — 89	11	3	2	6	8	2	3	3
Total	90	23	24	43	94	54	20	20

All age groups: $\chi^2 = 17.02$; degree of freedom $= 2$; $p = <0.01$.

Under 20 years of age: $\chi^2 = 13.18$; degree of freedom $= 2$; $p = <0.01$.

Over 20 years of age: $\chi^2 = 11.24$; degree of freedom $= 2$; $p = <0.01$.

Figure 5

Roentgenogram of the heart of a European child aged 10 with Fanconi's anemia. Extensive interarterial anastomoses are present.

cardial, myocardial, endocardial, or valvular disease. The coronary arteries were macroscopically completely free from atherosclerosis. The presence or absence of hypertrophy was determined by comparing the heart weight to body length with use of the tables of Zeek[25] and of Roessle and Roulet.[26] Furthermore, no adult hearts weighing more than 350 Gm. were included in the group.[27] On the basis of all these criteria 23 European hearts were classified as normal; 8 of these showed excellent anastomoses (35 per cent), and in the remaining 15 cases anastomoses were poor or absent. In the Bantu series 49 hearts were found to be normal; 54 per cent had excellent anastomoses and the remaining 23 hearts either showed poor or no evidence of anastomoses. These anastomoses were found in all age groups. It therefore appears that the anastomoses are present in both racial groups irrespective of concomitant heart disease, but that the normal hearts in the Bantu show a higher incidence of intercoronary arteriolar anastomoses than the European hearts.

Coronary Atherosclerosis and Coronary Anastomoses

The appraisal of the degree of coronary heart disease was based on the degree of least luminal patency at any specific point in the vascular tree. For this purpose the entire arterial tree (left and right coronary distribution) was transected at intervals of 3 to 5 mm. and the grading of Gore and Tejada[28] was applied with the following minor modifications: in those classified as grade 0 luminal patency was more than nine tenths normal; grade 1 indicated luminal patency of more than three quarters normal; grade 2 more than half normal; grade 3 more than quarter normal; and grade 4 less than quarter normal

total occlusion. The point of severest narrowing in either the left or right coronary tree was taken as an index of the degree of atheromatosis in the individual case. Since Zoll, Wessler, and Schlesinger[27] have shown that cases with slight coronary artery narrowing do not differ significantly in the degree of anastomoses from their control group with no narrowing, it was decided to compare the cases with group 0 and 1 narrowing with those classified as grades 2 to 4. The results obtained are shown in tables 4 and 5.

In the European group 17 of 58 cases having grade 0 and 1 narrowing showed "good" anastomoses (29 per cent); 32 cases were classified as having grade 2 to 4 atherosclerosis and 6 of these showed good anastomoses (19 per cent). The Bantu hearts with grade 0 to 1 luminal narrowing showed "good" anastomoses in 59 per cent of cases. In the small group of cases with severe narrowing, 4 showed comparable anastomoses, i.e., 44 per cent.

The number of European and Bantu cases with severe narrowing are too small to permit statistically valid conclusions but it seems as if the severity of the atherosclerosis had not influenced the development of coronary anastomoses to any marked degree. The small number of Bantu cases that could be classified as having severe atherosclerosis in the present study has again forcibly demonstrated that the Bantu do not develop the same degree of atherosclerosis as the European.

Myocardial Hypertrophy and Coronary Anastomoses

In this series only the hearts in the age groups above 20 years were considered. All hearts weighing more than 350 Gm. were regarded as hypertrophic.[27] In view of the small number of cases it was not possible to subdivide them according to the various causes of hypertrophy. As a result these cases included hypertensive hearts, cases of cor pulmonale, longstanding anemia, valvular disease, and in the Bantu group a few with idiopathic cardiac hypertrophy were also present. In the European group (table 6) 37 per cent of the cases had "good" anastomoses and in the Bantu group 71 per cent showed comparable anastomoses. The hypertrophic Bantu hearts showed a higher percentage of anastomoses than the control group, but the hypertrophied European hearts did not. However, one does not expect better communications, since Dock[29] has shown that the hypertrophic heart does not necessarily have an inadequate oxygen supply. Zoll et al.[27] had similar results before they took the fact of anemia into consideration. Their total group of hypertrophied hearts did not show a statistically significant difference in anastomoses from their control group until hearts from patients with anemia were removed from both groups.

Table 4

Luminal Narrowing and Anastomoses in European Hearts

Age group	Number of cases	Degree of luminal narrowing: grade 0—1	Degree of luminal narrowing: grade 2—4	Anastomoses in grade 0—1	Anastomoses in grade 2—4
0 — 9	6	6	–	2	–
10 — 19	10	10	–	2	–
20 — 29	10	9	1	4	–
30 — 39	11	8	3	2	–
40 — 49	10	9	1	3	–
50 — 59	10	6	4	1	1
60 — 69	10	5	5	2	–
70 — 79	12	2	10	–	3
80 — 89	11	3	8	1	2
Total	90	58	32	17	6

$\chi^2 = 1.21$; degree of freedom $= 1$; $p = 0.30\text{-}0.20$.

Discussion

The most significant observation in the present investigation has been the consistently higher frequency of interarterial coronary anastomoses shown by Bantu hearts as compared with European hearts. This difference has been present irrespective of hypertrophy or coronary arterial disease, despite more severe atherosclerosis in the older European hearts. It has therefore been established that the difference cannot be explained on the basis of any acquired intrinsic organic heart disease or to differences in the gross anatomic vascular pattern.

It has, however, been clearly established in humans,[1, 27, 30] and also in experimental ani-

Table 5

Luminal Narrowing and Anastomoses in Bantu Hearts

Age group	Number of cases	Degree of luminal narrowing grade 0—1	Degree of luminal narrowing grade 2—4	Anastomoses in grade 0—1	Anastomoses in grade 2—4
0 — 9	10	10	–	7	–
10 — 19	10	10	–	10	–
20 — 29	10	10	–	5	–
30 — 39	11	11	–	6	–
40 — 49	14	14	–	9	–
50 — 59	11	9	2	5	1
60 — 69	10	8	2	3	–
70 — 79	10	7	3	4	2
80 — 89	8	6	2	1	1
Total	94	85	9	50	4

$\chi^2 = 0.69$; degree of freedom $= 1$; $p = 0.30$-0.50.

mals,[31-33] that cardiac anoxia stimulates the development of intercoronary arteriolar anastomoses. Of the factors that have been cited as causing cardiac anoxia, such as coronary heart disease, cor pulmonale, valvular disease, cardiac hypertrophy, and anemia,[27] only the latter factor need be considered in a group of people in whom anastomoses are present from a very early age and in whom it persists throughout adult life. This is, however, difficult to prove, since hemoglobin estimations at the time of death obviously have limited values and may be misleading. The time required for anastomoses to develop is not known with certainty, and whether these anastomoses are permanent has not yet been conclusively proved. Furthermore, since both our own and the findings of Laurie and Woods[2] indicate that these anastomoses develop at a very early age, one would expect anemia to be prevalent among the Bantu during infancy and childhood. Until fairly recently no data were available in this respect, but at the beginning of 1959 Lanzkowsky and McKenzie[34] published their results of a survey carried out to determine the incidence of iron-deficiency anemia in pre-school Coloured and Bantu children in Cape Town. They found the incidence of anemia to be 65 per cent for Coloured children and 67 per cent for African children.

At Baragwanath non-European hospital, Metz and Stein[35] found iron-deficiency anemia

Table 6

Relationship between Cardiac Hypertrophy and Anastomoses

Heart weight	European HH*	European HHcA†	Bantu HH	Bantu HHcA
350—449	17	6	8	6
450—549	7	3	5	4
550 +	6	2	4	2
Total	30	11	17	12

*Hypertrophic hearts without anastomoses.
†Hypertrophic hearts with anastomoses.

to be common among Bantu infants and they reported the highest incidence to be between 6 and 18 months of age. They, furthermore, stress the importance of kwashiorkor as a possible etiologic factor.

With regard to megaloblastic anemia, Walt et al.[36] reported an incidence of 9 per cent in Bantu infants admitted to a Durban hospital. These findings have also been confirmed by Cassel and Metz,[37] who stated that megaloblastic anemia was "common in Bantu infants."

From the foregoing data it is obvious that iron-deficiency anemia and megaloblastic anemia are prevalent among Bantu infants and children. In view of the experimental data available, it seems justifiable to propose that these diseases are responsible for the higher incidence of intercoronary anastomoses in normal Bantu than in European hearts in this series. Zoll, Wessler, and Schlesinger,[27] with a somewhat similar technic, found an incidence of anastomoses of 9 per cent in a group of normal hearts from whom patients with anemia had been removed. A high incidence of anemia in the control group of this series may well obscure the effects of other factors on anastomoses; for example, the failure to find an effect of hypertrophy on anastomoses in the European group and an effect of increasing degrees of coronary arterial narrowing, which are contrary to the results of Zoll et al.,[27] may be accounted for on this basis.

Although the present study has confirmed the findings of Laurie and Woods[2] of a high incidence of coronary anastomoses in Bantu

hearts, the clear-cut differences of the anastomotic pattern in the ethnic groups studied invalidate the conclusions of the latter authors, that "a majority of healthy people have functionally important inherited coronary anastomotic blood supply."

The lower incidence of the severer degrees of coronary atherosclerosis in the Bantu is reemphasized in this investigation and, therefore, a firm conclusion is not possible as to what extent the better anastomotic circulation protects the Bantu heart against ischemic heart disease.

Summary

The coronary arterial pattern and coronary anastomoses have been investigated in 90 European and 98 Bantu hearts.

A significantly better coronary anastomotic blood supply has been demonstrated in Bantu hearts. This was found to be present from a very early age onward and not related to hypertrophy, atherosclerosis of the coronary arteries, or to gross anatomic differences of the arterial tree, such as a third primary division of the left coronary artery. The latter was found to be more common (74 per cent) in Bantu than in European hearts (38 per cent).

It is suggested that the reason for the better anastomoses might be the high incidence of megaloblastic and iron-deficiency anemia in Bantu children.

The low incidence of the severe degrees of coronary atherosclerosis and its complications has been reaffirmed in the Bantu hearts.

Acknowledgment

The authors acknowledge, with appreciation, the criticisms of Professor J. Barnetson. Professor C. J. N. Loubser has kindly provided us with some hearts from the Medico-Legal Laboratories. We are indebted to Professor D. G. Halet for the statistical analyses and to Mr. C. J. de Swardt for the photomicrography.

Summario in Interlingua

Le configuration del arterias coronari e le grado del anastomoses coronari esseva investigate in le cordes de 90 europeos e de 98 bantus.

Un significativemente melior provision anastomotic de sanguine coronari esseva demonstrate in le cordes bantu. Esseva trovate que isto esseva presente depost le etates le plus juvene e que le phenomeno non esseva relationate a hypertrophia, atherosclerosis del arterias coronari, o macrodifferentias anatomic del vasculatura arterial, como per exemplo un tertie division primari del arteria sinistro-coronari. Iste tertie division esseva plus commun in cordes bantu que in cordes europee (74 e 38 pro cento, respectivemente).

Es opinate que le explication del plus efficace anastomoses in le cordes bantu jace possibilemente in le plus alte incidentia de anemia megaloblastic e anemia a carentia de ferro in le infantes bantu.

Le studio ha confirmate le basse incidentia de sever grados de atherosclerosis coronari e de su complicationes in le cordes del bantus.

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On Cardiac Murmurs

By AUSTIN FLINT, M.D.

The practiced auscultator, by listening to the murmurs alone, is able to tell whether lesions are situated at the mitral, or at the aortic, or at the pulmonic orifice, and he is able to say, in certain cases, that the valves which are to protect these orifices against a regurgitant current of blood, have been rendered by disease inadequate to their office.—*Am. J. M. Sc.* n.s. 44: 29, 1862.

Electrocardiographic Changes Simulating Myocardial Ischemia and Infarction Associated with Spontaneous Intracranial Hemorrhage

By G. J. Cropp, M.D., and G. W. Manning, M.D.

ALTHOUGH a number of reports have appeared in the literature describing nonspecific S-T and T-wave changes in the electrocardiogram associated with neuromuscular disorders[1] electrolyte disturbances, hypoxemia, postprandial effects, etc., relatively few have appeared describing electrocardiographic changes, associated with intracranial hemorrhage. In 1947 Byer et al.[2] described transitory changes (9 days) with large upright T waves and prolonged Q-T intervals in a patient with subarachnoid hemorrhage. In an extensive review of nonspecific T-wave changes Levine, in 1953, reported a case[3] of subarachnoid hemorrhage which, at postmortem examination, was found to be due to a ruptured aneurysm in the circle of Willis. Although electrocardiographic changes considered to be associated with myocardial infarction were present in this case, the heart was found to be normal at postmortem examination. Levine[3] also referred to experimental studies of Beattie et al., who stimulated the basal ganglia and produced cardiac arrhythmias, and of Dikshit, who by intraventricular injection of caffeine produced ventricular extrasystoles with the associated S-T segment and T-wave changes. Levine concluded that the irregularities in rhythm were probably on the basis of vagal stimulation. In a very complete review of the literature Fulton[4] summarized the effect of frontal lobe stimulation. The area that appears to be most intimately linked with the cardiovascular system was the orbital surface of the frontal lobe (area 13) and the anterior cingulate gyrus (area 24). The result of stimulation was a rise or fall in blood pressure and alterations in heart rate. Respiration was also affected when area 13 was stimulated. Evidence was quoted that area 13 contains the chief cortical representation of the vagus nerve. This would appear to favor Levine's assumption of the vagal origin of the arrhythmias. Kaada[5] studied the autonomic responses with stimulation of the ventral and medial aspect of the cerebral hemispheres. He, too, recorded inhibition of respiratory movements, slow increase of blood pressure, or sudden drop of blood pressure upon stimulation of the orbital surface of the frontal lobe. In neither of these studies, however, were electrocardiographic variations discussed.

Burch, et al.[6] drew attention to T-wave abnormalities and long Q-T intervals in patients suffering from cerebral hemorrhage, subarachnoid hemorrhage, and a group of unclassified cerebrovascular accidents. The increase in the Q-T interval was from 7 to 66 per cent above normal. The T waves were described as large, were similar to those seen in early myocardial ischemia, and were reported to revert to normal with improvement of the clinical condition, or changed to the pattern of any underlying heart disease present prior to the intracranial insult. These authors also described prominent U waves. It was their opinion that the large U waves contributed frequently to the height of the T waves. These investigators emphasized that subarachnoid hemorrhages were particularly liable to produce these abnormal patterns, realizing at the same time that other types of intracranial disease also may cause T-wave abnormalities.

Wasserman et al.,[7] in 1956, discussed elec-

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Table 1

Summary of Clinical Literature

Authors	No. of cases	Intracranial lesions	No. of cases having heart disease	Autopsy, heart	Electrocardiogram
Byer, Ashman, and Toth (1947)	5	4 Cerebrovascular accident; 1 hypertensive encephalopathy	4	?	Large upright T waves; long Q-T interval
Levine (1953)	1	Subarachnoid hemorrhage	0	Normal	Myocardial infaret
Burch, Meyers, and Abildskov (1954)	17	Cerebral hemorrhage; subarachnoid hemorrhage; unclassified cerebrovascular accident	?	?	Large, wide T waves; long Q-T interval; prominent U waves
Wasserman, Choquette, Cassinelli, and Bellet (1956)	12	Subarachnoid hemorrhage; intracerebral hemorrhage; subdural hematoma; cerebral edema; cerebral thrombosis	11	1 case myocardial infaret	Long Q-T interval; deep, wide T-wave inversion; prominent U waves
Cropp and Manning (1960)	29	Subarachnoid hemorrhage	9	5	RS-T segment and T-wave changes

trocardiographic changes in 12 patients with acute cerebrovascular accidents, 11 of whom had evidence of previous heart disease. Prolonged Q-T intervals, inverted widened T waves and prominent U waves were described. They suggested interference with the cardiovascular inhibitory and augmentory centers in the medulla oblongata. The clinical literature, which we have reviewed in connection with this study, is summarized in table 1.

Our interest in electrocardiographic patterns simulating myocardial infarction or ischemia in cases of subarachnoid hemorrhage was aroused in 1956, when a case of subarachnoid hemorrhage, proved by bloody spinal fluid and cerebral angiogram revealed a classical pattern of anterior cardiac infarction in the electrocardiogram, taken during routine investigation, prior to hypothermia and surgical treatment (fig. 1). Surgical treatment was delayed because of these findings and the patient suffered further intracranial hemorrhage and succumbed. At postmortem examination the heart was completely normal with patent coronary arteries and no evidence of coronary atherosclerosis, or old or recent infarction. At approximately the same time an exactly similar incident occurred at another center. We recalled a similar case in 1949 in which a subarachnoid hemorrhage had occurred, and in which the electrocardiogram was indicative of myocardial infarction or severe myocardial ischemia. Apart from this, no evidence of heart disease and a completely clear history was obtained. This patient was managed conservatively without surgical treatment and made an uneventful recovery with no recurrence of cerebrovascular difficulty. She has continued well to the present time with no evidence of heart disease.

Clinical Material

Since 1956 we have studied several cases of subarachnoid hemorrhage in which the electrocardiogram was suggestive of myocardial ischemia, although no symptom or clinical signs of heart disease could be found. A total of 29 cases of subarachnoid has been studied. Preoperative electrocardiograms were recorded in all, and in many serial tracings have been obtained. The ages, in this series, ranged from 26 to 67 years. Eighteen of the 29 cases were female, and 11 were male. All had bloody cerebrospinal fluid, and a definite diagnosis of spontaneous intracranial hemorrhage

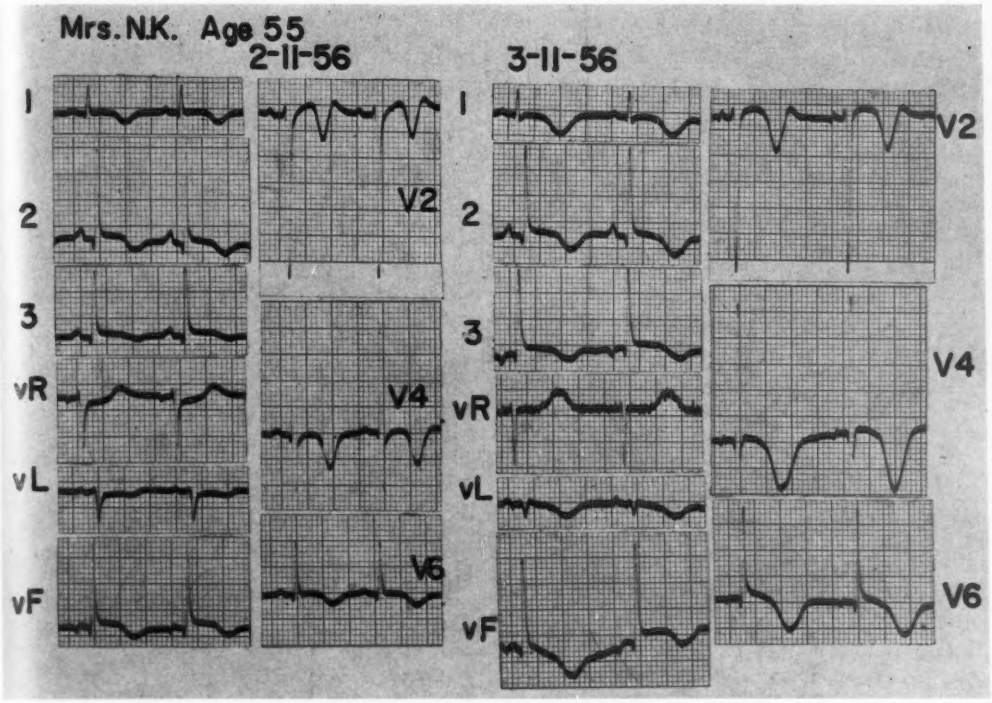

Figure 1

Case 2, Mrs. N. K., age 55. Electrocardiograms shortly after onset of spontaneous intracranial hemorrhage reveals a pattern of recent myocardial infarction. Postmortem findings revealed normal heart and coronary arteries.

was made. All but the first case in 1949 had carotid angiography performed prior to surgery. Twenty-two of the 28 cases who underwent angiography exhibited a definite site of bleeding. Nineteen of the 29 patients were subjected to craniotomy. Eight of the 29 cases have died since the beginning of this study, and 5 of the 8 were studied at postmortem examination.

Electrocardiographic Findings

In preoperative tracings after intracranial hemorrhage the heart rate was variable being recorded at 59 or less in 4 patients, 60 to 100 in 23, and 101 or more in 2 cases. Wandering pacemaker was observed in 2, nodal rhythm in 1, nodal extrasystoles in 1, and ventricular extrasystoles in 3 cases. Normal P waves were found in 25 cases, spiked P waves in 3 and in

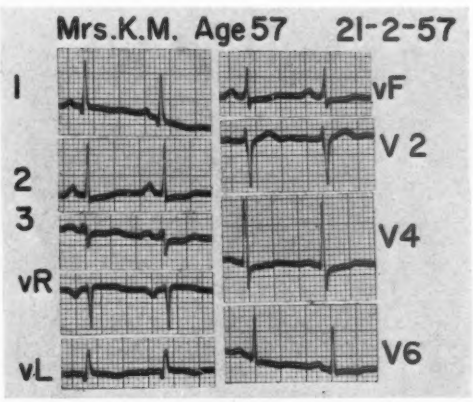

Figure 2

Case 5, Mrs. K. M., age 57. Preoperative electrocardiogram shows RS-T changes in patient with subarachnoid hemorrhage. Normal heart postmortem.

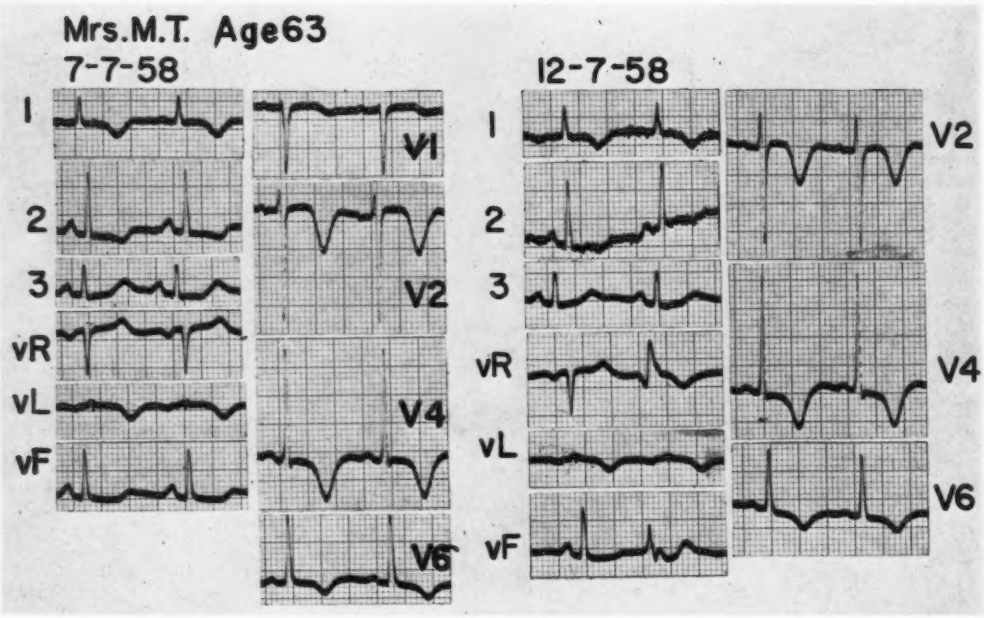

Figure 3

Case 4, Mrs. M. T., age 63. Serial preoperative tracings with obvious abnormal T patterns suggestive of severe ischemia or recent infarction.

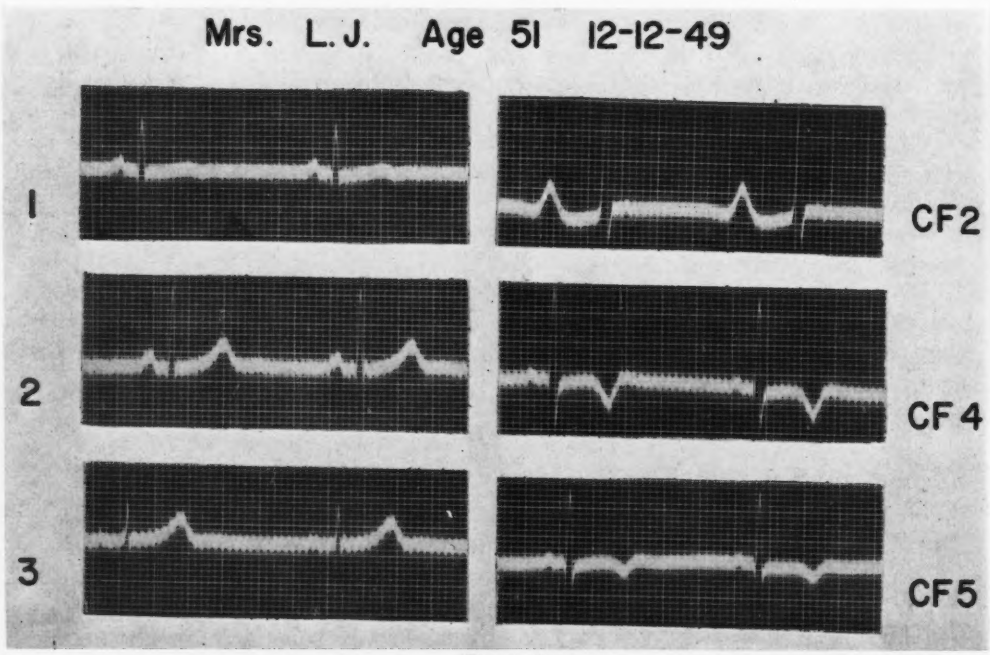

Figure 4

Case 1, Mrs. L. J., age 51. Proved subarachnoid hemorrhage. Electrocardiographic pattern indicative of anterolateral ischemia without RS-T segment or QRS changes.

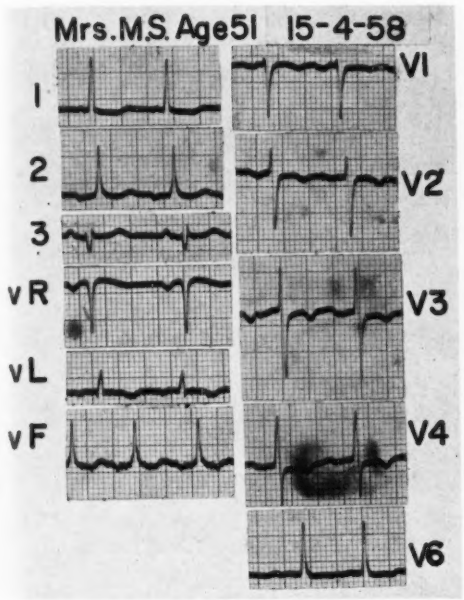

Figure 5

Case 13, Mrs. M. S., age 51. Proved subarachnoid hemorrhage. Electrocardiographic pattern suggestive of myocardial ischemia or recent infarction in patient who showed a completely normal heart and coronary arteries at postmortem examination.

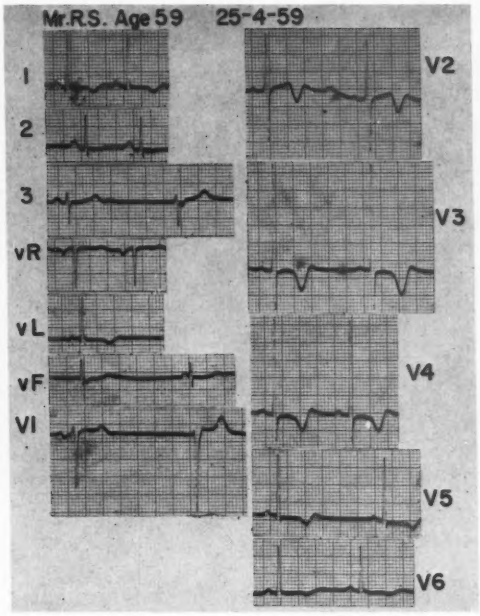

Figure 6

Case 27, Mrs. R. S., age 59. Proved subarachnoid hemorrhage. Tracing shows left ventricular hypertrophy with additional T-wave changes suggestive of recent myocardial ischemia. A wandering pacemaker is also present.

Table 2

Duration of Q-T Intervals in Patients with Subarachnoid Hemorrhage

	Total group	Patients with abnormal electrocardiographic patterns
Q-T interval short	5	3
Q-T interval normal	10	2
Q-T interval long	14	10
	29	15

(nodal rhythm) P waves were absent. The -R interval varied from 0.10 (rapid rate) to 18 second and was considered to be within ormal limits. Duration of QRS was normal 28 cases and ranged from 0.04 to 0.10 econd. In 1 case (nodal rhythm and right undle-branch block) QRS duration was 0.12 econd. Left axis deviation was present in 10 ases and right in 1. Two cases with left axis eviation revealed a pattern of left ventricular hypertrophy, and 2 others (with left axis deviation) revealed questionable evidence of left ventricular hypertrophy. Four tracings revealed abnormal or questionable Q waves in leads II, III, and aV_F. High voltage of the QRS complexes were present in 6 cases, 4 of which revealed other electrocardiographic evidence of left ventricular hypertrophy; 1 revealed a pattern of right bundle-branch block, and 1 left axis deviation without other evidence of left ventricular hypertrophy.

Byer and associates[2] have reported Q-T interval prolongation in subarachnoid hemorrhage. In this study Q-T intervals were measured and corrected for age, sex, and heart rate.[8] In 67 per cent of tracings suggestive of myocardial damage abnormally long Q-T intervals were found (table 2).

The observations of wave amplitudes and time intervals for each of the 28 cases studied are shown in table 3. RS-T elevation or depres-

Table 3

Electrocardiographic Measurements

No.	Age and sex	Heart rate	P-R	Axis deviation	QRS	Q-T	RS-T	T-wave amplitude (mm.) T_1	T_2	T_3	aV_R	aV_L	aV_F	V_1	V_2	V_3	V_4	V_5	V_6	U wave	Comments
1	51F	53	0.16	N	0.08	N	N	+0.3 −0.2	4	3.5					CF_2 5		CF_4 −5	CF_5 −2		0	Primary T changes; ? recent ischemia
2	55F	83	0.14	N	0.08	L	L3, aV_F, V_2 ↑	−2	−2	−0.5	2	−1	−1.5		−6.5		−6		−2	0	Serial tracings with pattern of recent infarction
3	40M	60	0.16	N	0.10	L	N	0	2	2	−0.5	−1	1.5		10		+1 −1.5		+0.5	3+	Anterior wall ischemia
4	63F	83	0.16	N	0.06	L	cove	−3	−2	1	2	−2	−1	−1	−8		−7		−2	0	Recent infarction, serial tracings
5	45F	88	0.16	L	0.08	L	N	−0.5	+0.5	1.5	0	−1	1		CF_2 8		CF_4 4		CF_6 −1.5	1+	Hypertensive left ventricular hypertrophy
6	51F	56	0.14	N	0.10	S	L1 ↓ L3 ↑	0.5	1.5	0.5	−1	0.5	0.5	0.5	1.5	1	1	0.5	0.5	2+	Suggestive of recent infarction
7	66M	75	0.16	L++	0.08	S	N	2	2.5	1.5	−3	0	1.5	−1.5	2.5	3	4.5	2.5	2	2+	Frequent nodal extrasystoles otherwise normal
8	53F	60	0.14	L	0.06	N	N	1	0	−1	0	1	−0.5		−2		−1		0	1+	Serial tracing; ischemic T waves; post-op. tracing suggestive of further myocardial damage
9	26F	45	0.18	N	0.08	N	N	4	5	1	−4	1	2.5	−1.5	4.5	5	6	5	5	1+	Tall T waves; bradycardia
10	48F	83	0.18	N	0.08	L	N	0	1	1	0	0	0.5		4.5		1		−0.5	2+	Vertical heart; left ventricular hypertrophy
11	67F	75	0.16	L	0.08	L	N	2	3.5	1.5	−2.5	0	+2		+1 −1		2.5		3	1+	Left ventricular hypertrophy
12	45F	100	0.14	N	0.06	S	N	1	1.5	0	−1	1.5	0.8	−1	1.5		2		1	1+	Normal. Operative tracing abnormal
13	51F	100	0.10	L	0.06	N	L1, V_4, L3 ↓↑	−1	0.5	0.5	0	−1	1	0	0		0		0	1+	Serial changes suggestive of recent infarction
14	40F	83	0	N	0.12	L	L1, L2, 3, aV_F ↓	5.5	−5	−8	2	7	−7	1	6	6	7	8	6	1+	R.B.B.B. and serial changes

15	57F	100	0.16	L	0.06	S	L2, 3, aV_F, V_{4-6}	↓	−0.3	0.3	1	0	−0.4	0.4		1.5		−0.4		0.3	1+	Suggestive of recent infarction
16	63F	100	0.18	R	0.08	L	V_{2-4}	↑	−1	1	1.5	−0.5	−2	1.5	0.3	−2	−2	−2.5	−1.5	−1	1+	Serial tracings segment elevation of coronary type
17	54M	82	0.16	L	0.06	N	L2, aV_F, V_6	↓	1	2	1	−1.5	0	1		3		5		1	3+	Quest. L.V.H.
18	51M	80	0.16	N	0.08	L	L2, 3	↑	−0.5	3	3	−1.5	−1.5	4		4		4		0.5 −0.5	1+	Ischemic T pattern
19	47M	85	0.14	N	0.08	N	N		1	1.5	0.5	−1.5	0	1.5		0.5		2.5		1.5	0	Normal
20	34F	94	0.10	N	0.04	N	N		1	1	0	−1.5	0.5	0.3		1.5		1.5		1	1+	Normal
21	67F	115	0.14	N	0.08	N	L2, 3, aV_F, V_2	↓↑	1.5	1	0	−1.5	1	0.5		4		2.5		1	0	Questionable ischemic segment changes, likely due to tachycardia
22	67M	150	0.10	N	0.06	L	L2, 3, aV_F, V_{4-5}	↓	0.3	5	4	−0.5	0	4	6	5	6	6	4	3	?	Tachycardia causing segment changes and ischemia?
23	34F	75	0.16	N	0.06	L	N		1	2	1.5	−1	0	1.5		2.5		3		1.5	1+	Q-T interval prolonged
24	26M	71	0.16	N	0.08	N	N		1.5	2.5	1	−2	0.3	1	3	9	8	6	3	2.5	1+	Normal
25	46M	94	0.12	L	0.06	L	L1, aV_L, L3	↓↑	0.3	0.3	0	−0.5	0.3	0.2	1	2	1.5	0.5	0	0	1+	Serial changes Q-3 T-3 pattern suggestive of recent infarction
26	26M	50	0.16	N	0.06	N	N		3	2	−1	−2	2	1	−1.5	4.5	5	4	4	2.5	2+	Bradycardia
27	59M	85	0.12 to 0	L	0.06	L	$V_{3, 4, 6}$ $V_{1, 2}$	↓↑	−1	0	2	1	−1.5	1	2	−4	−6	−5	−1 +1	−0.5	1+	Wandering pacemaker; left ventricular hypertrophy with superimposed T-wave changes in mid precordium; Serial tracings—infarction?
28	60M	70	0.16	L	0.06	N	N		1.5	1.5	+0.5 −0.5	−1	1	0.5		1.5		6		2	2+	Normal
29	54F	75	0.16	N	0.08	L	L1, 2, V_{4-6}, V_1	↓↑	1	1.5	0.5	−1	−0.5	0.5	−0.5	2	1.5	1	0.5	0.5	3+	S-T and T-wave changes suggestive of myocardial damage. Post-op. tracings show questionable left ventricular hypertrophy only. Heart 430 grams —post mortem

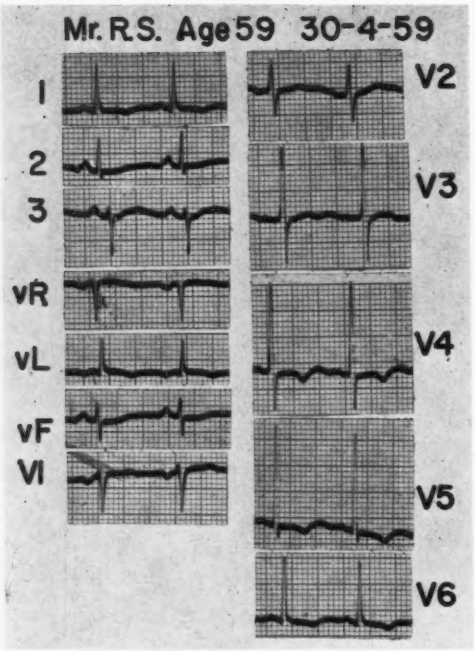

Figure 7

Case 27, Mrs. R. S., age 59. Same case as shown in figure 6. Tracing taken 5 days later and showing regression of T-wave abnormalities and sinus rhythm.

sion was observed in 13 cases (figs. 1 and 2), 11 of which were considered to be suggestive of a recent injury pattern (fig. 3).

Sixteen of 29 tracings showed T-wave abnormalities (fig. 4) most frequently seen in leads I, aV_L, the mid and lateral precordial leads. Fourteen of the 16 tracings showed very low or negative T waves in lead II. Twelve of these were associated with abnormalties in other leads or questionable segment changes and 2 with patterns of left ventricular hypertrophy. Of these 14 low or negative T_1 patterns, 5 were flat to 0.5 mm. in height, whereas 9 were negative, the most negative deflection being 3 mm. (table 3). One case had nodal rhythm with right bundle-branch block and showed progressive changes in postoperative tracings. Thus 15 tracings showed T-wave changes indicative of myocardial ischemia (table 3). Additional examples of T-wave abnormalities are shown in figures 5 to 7.

Burch et al.[6] reported abnormally large U waves in cerebrovascular accidents. Twenty-four patients in this series showed U waves, 8 of which were considered to be abnormally large. Three of the 15 with abnormal T waves showed abnormally large U waves (fig. 8). The electrocardiographic and clinical findings are summarized in tables 3 and 4.

Discussion

There appears to be only 1 case in the literature[3] in which a diagnosis of myocardial infarction, confirmed by electrocardiography, was made in a patient with a ruptured aneurysm in the circle of Willis, and a normal heart was observed post mortem. Others[2, 6, 7] have drawn attention to isolated electrocardiographic abnormalities. The results of the study reported here support the findings of Wasserman et al.,[7] who described T-wave inversion and prominent U waves. T-wave abnormalities were the most pronounced and most frequent abnormalities in the 29 cases reported here. Sixteen of 29 cases showed abnormal T waves. Increased T-wave amplitude as described by Byer et al.[2] and Burch and his co-workers[6] were not prominent in this study. In the group with ischemic or infarct-like patterns two thirds of the patients showed prolonged Q-T intervals, previously described by Byer et al. and others.[2, 6] The heart rate and rhythm revealed no characteristic pattern. Bradycardia was more common than tachycardia. The rhythm was of sinoatrial origin in 22 of the 29 cases. P waves and P-R intervals likewise revealed no abnormalities of importance. Two of the 10 cases with left axis deviation were associated with left ventricular hypertrophy, 2 with questionable left ventricular hypertrophy, 2 with otherwise normal tracings, 4 with ischemic or infarct-like tracings, but no indication of left ventricular hypertrophy. Left axis deviation did not show any correlation with spontaneous intracranial hemorrhage. Abnormality of the QRS complex was dependent on underlying heart disease but

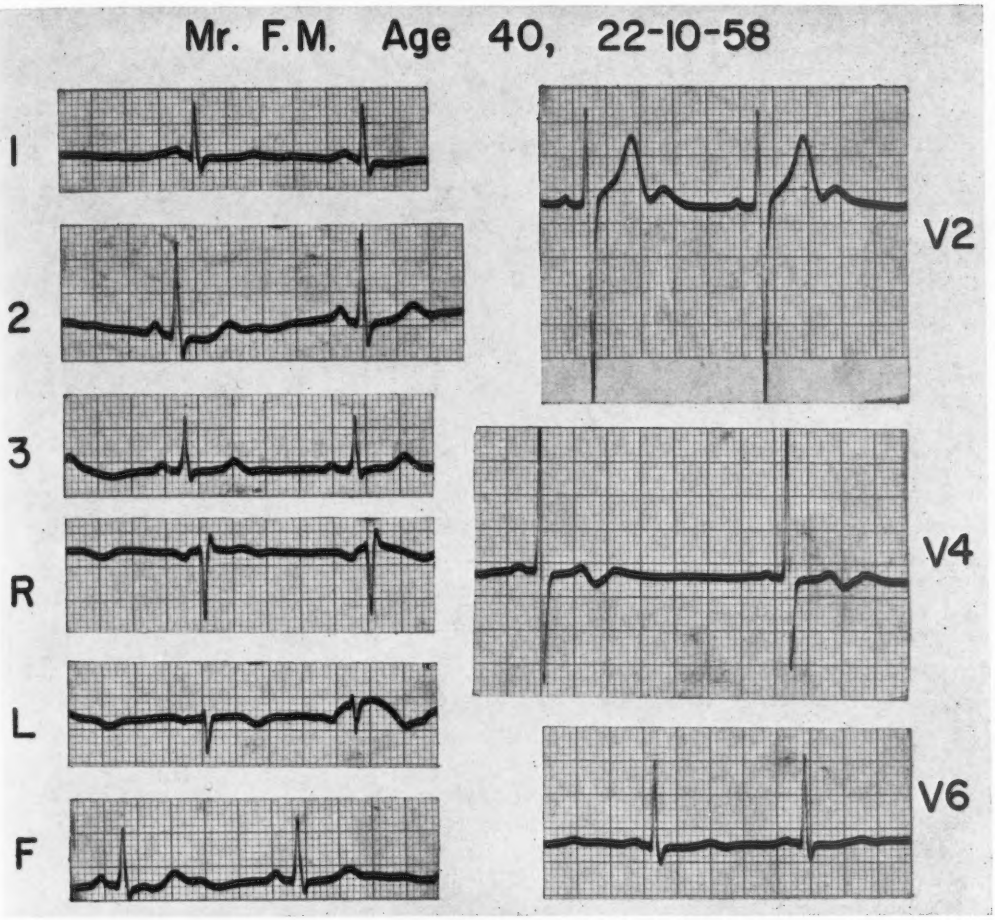

Figure 8

Case 3, Mr. F. M., age 40. Spontaneous intracranial hemorrhage. Electrocardiogram shows abnormally large U waves particularly in V_1 and V_4 along with T-wave changes suggestive of myocardial ischemia.

did not contribute any identifying characteristic of the tracings studied in this series.

The most prominent features in this study were RS-T segment changes and T-wave abnormalities. We think that many of these changes are directly related to intracranial hemorrhage, since they appeared in the presence of normal cardiovascular findings. Although postmortem confirmation is by no means complete, this assumption is substantiated by 4 postmortem examinations. The fifth autopsy was on a patient not exhibiting the electrocardiographic abnormalities. The 4 patients with electrocardiographic changes, who succumbed from subarachnoid hemorrhage revealed at postmortem examination the site of intracranial bleeding but no evidence of myocardial infarction or coronary artery narrowing. One of the 4 had a hypertensive heart of 430 Gm. but the coronary vasculature was normal. We considered the changes as indicative of recent infarction or ischemia because of the absence of Q waves, and the frequent association of RS-T segment devia-

Table 4

Clinical Features

No.	Patient	Age and sex	Cerebrospinal fluid	Site of lesion	Craniotomy	Signs of heart disease	Symptoms of heart disease	Autopsy, brain	Autopsy, heart
1	(L.J.)	51F	Bloody	No angio	No	No	No	Alive	Alive
2	(N.K.)	55F	Bloody	R. int. carotid at post. communicating	No	No	No	Aneurysm confirmed	Normal
3	(F.M.)	40M	Bloody	Ant. communicating	Yes	No	No	Dead, no P.M.	Dead, no P.M.
4	(M.T.)	63F	Xantho-chromic	R. int. carotid at post. communicating	Yes	Soft systolic murmur	No	Alive	Alive
5	(M.M.)	45F	Bloody	Ant. communicating	Yes	BP 240/130; Gallop rhythm; heart enlarged	No	Aneurysm confirmed	Coronary atherosclerosis; old myocardial infaret
6	(M.S.)	51F	Bloody	R. int. carotid	Yes	No	No	Alive	Alive
7	(E.S.)	66M	Bloody	Negative	No	No	No	Alive	Alive
8	(A.T.)	53F	Microscopic blood	Negative	Yes	No	No	Alive	Alive
9	(M.K.)	26F	Bloody	Ant. communicating	No	No	No	Alive	Alive
10	(J.G.)	48F	Xantho-chromic bloody	Negative	No	B.P. 180/120	Palpitation	Alive	Alive
11	(L.C.)	67F	Xantho-chromic	R. int. carotid	No	X-ray—cardiac enlargement	No	Alive	Alive
12	(K.R.)	45F	Bloody	R. ant. cerebral	Yes	No	No	Alive	Alive
13	(M.S.)	51F	Bloody	R. int. carotid at post. communicating	Yes	No	No	Aneurysm confirmed	Normal
14	(J.L.)	40F	Bloody	Ant. communicating	Yes	BP 210/110	No	Alive	Alive
15	(K.M.)	57F	Bloody	L. int. carotid at post. communicating	Yes	No	No	Aneurysm confirmed	Normal
16	(F.W.)	63F	Bloody	R. int. carotid at post. communicating	Yes	BP 170/110; congestive failure?	Shortness of breath, ankle edema, orthopnea	Alive	Alive
17	(R.M.)	54M	Bloody	Negative	Negative exploration	BP 180/105; extrasystoles	Myocardial infaret, 3 yrs. ago; dyspnea not requiring digitalis	Alive	Alive
18	(A.N.)	51M	Bloody	Basilar artery	Yes	No	No	Alive	Alive
19	(H.C.)	47M	Bloody	Negative	No	No	No	Alive	Alive
20	(I.Mc.)	34F	Bloody	L. int. carotid	No	No	No	Alive	Alive
21	(E.D.)	67F	Bloody	Negative	No	No	No	Alive	Alive
22	(S.Y.)	67M	Bloody	Negative	No	BP 230/125; no cardiac enlargement	No	Dead, no P.M.	Dead, no P.M.

24	(J.K.)	26M	Bloody	L. middle cerebral at trifurcation	Yes	Gr. II systolic murmur; BP 130/80; no mitral stenosis	No	Alive	Alive	
25	(J.K.)	46M	Xantho-chromic	L. ant. cerebral	Yes	No	No	Alive	Alive	
26	(J.B.)	26M	Bloody	R. ant. cerebral	Yes	No	No	Alive	Alive	
27	(R.S.)	59M	Bloody	L. medial supra-clinoid carotid	Yes	BP 150/90	History hypertension; no failure	Alive	Alive	
28	(N.J.)	60M	Bloody	L. int. carotid	Yes	Systolic murmur (Gr. I)	No	Alive	Alive	
29	(R.O.)	F	Bloody	1. R. ant. cerebral L. horizontal part. 2. L. middle cerebral. 3. R. int. carotid	Yes	No	No	Aneurysm confirmed		Weight 430 Gm.; vessels normal

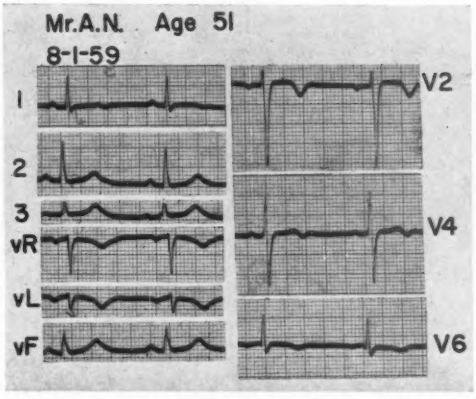

Figure 9

Case 19, Mr. A. N., age 51. Spontaneous intracranial hemorrhage from basilar artery aneurysms. Borderline electrocardiographic changes suggestive of myocardial damage.

tions. Thirteen of the 15 abnormal patterns showed flat or negative T waves in lead I. This appeared to be the most characteristic abnormality. This finding is suggestive of recent myocardial infarction, particularly when associated with RS-T segment and T-wave changes in other leads, as in this study. These tracings differ from those changes associated with left ventricular hypertrophy by absence of S-wave abnormalities in V_1, V_2, and possibly V_3, and lack of high QRS amplitude. The 2 tracings interpreted as simulating infarction without T-wave abnormalities in lead I showed in one case T-wave abnormalities in V_4 and V_6 and in the other right bundle-branch block and nodal rhythm with deep S, inverted T waves in leads II, III, and aV_F, together with segment depression in leads II, III, and aV_F. Figure 9 is an example of borderline abnormality that raises suspicion of myocardial damage.

It is of considerable importance that electrocardiographic abnormalities in patients with spontaneous intracranial hemorrhage are not misinterpreted. We have once been misled into a diagnosis of myocardial infarction on the basis of the electrocardiogram (fig. 1) in

Table 5

Location of Cerebral Lesions

No angiogram	1
Right internal carotid	6
Anterior communicating	2
Left internal carotid	2
Left anterior cerebral	1
Basilar	1
Negative angiogram	2
Total	15

a patient with spontaneous intracranial hemorrhage, and in whom surgical treatment was not carried out because of this diagnosis. In this case the heart was completely normal. Without a good history or clinical findings of heart disease, an electrocardiogram showing changes suggestive of recent infarction or acute myocardial ischemia should be interpreted as indicative of intracranial rather than of heart disease. Many more patients are now having electrocardiograms taken preoperatively because of the use of hypothermia in brain surgery. Hypothermia undoubtedly places considerable strain on the heart and may prove fatal to a patient with acute myocardial infarction. In this study it has been shown that the electrocardiographic changes are most suggestive of anterior myocardial ischemia or infarction. Some of the tracings shown in earlier papers describing electrocardiographic abnormalities associated with cerebrovascular accidents are similar to many of the tracings in this study; however, the similarity of their tracings with those of recent myocardial infarction or ischemia were not discussed. The study of 1 case (K.R.) raises the possibility of a center in the vicinity of area 13 in the frontal lobe, which may be responsible for abnormalities in the electrocardiogram. This patient had a normal electrocardiogram preoperatively. The patient was cooled as usual without change in the electrocardiogram. When the surgeon manipulated the carotid arteries and area 13, where the aneurysm was situated (right anterior cerebral artery), the electrocardiogram became grossly abnormal, the changes probably being associated with an ectopic multifocal ventricular rhythm (fig. 10). When surgical manipulation of the carotid arteries and the site of hemorrhage was completed, the electrocardiogram returned to normal. This patient's electrocardiogram is not included in the group of abnormal tracings because no abnormalities were present preoperatively. It would be of interest to investigate the possibility of a center in this vicinity that may be responsible for the electrocardiographic changes. Correlation of the site of the lesion to the electrocardiographic abnormalities (table 5) shows that in 11 of the 15 cases the point of bleeding was located in the anterior fossa (table 5). One case had the bleeding point in the posterior fossa. The electrocardiogram of this case shows mild but nevertheless definite changes (fig. 10). Two of the 15 cases had no bleeding point demonstrated and 1 case had no angiogram. Although the carotid arteries and their immediate branches are the usual site of aneurysms, it is apparent that electrocardiographic abnormalities are more frequently associated with subarachnoid hemorrhage than any other intracranial catastrophe. Therefore, the hypothesis may be proposed that the described electrocardiographic abnormalities are lesions in the cerebral cortex of the orbital surface of the frontal lobes (area 13) in the vicinity of the carotid siphons, the anterior communicating artery, and the anterior cerebral arteries. These studies support the view that electrocardiographic abnormalities may be related to vagus stimulation, since the vagus has cortical representation in area 13,[16] and since in one of our cases irritation of the vagus trunk in the vicinity of the carotid body and area 13 appeared to produce abnormalities similar to those described by Fulton.[4] It is possible that lesions other than bleeding aneurysms in the areas under discussion could produce similar electrocardiographic changes.

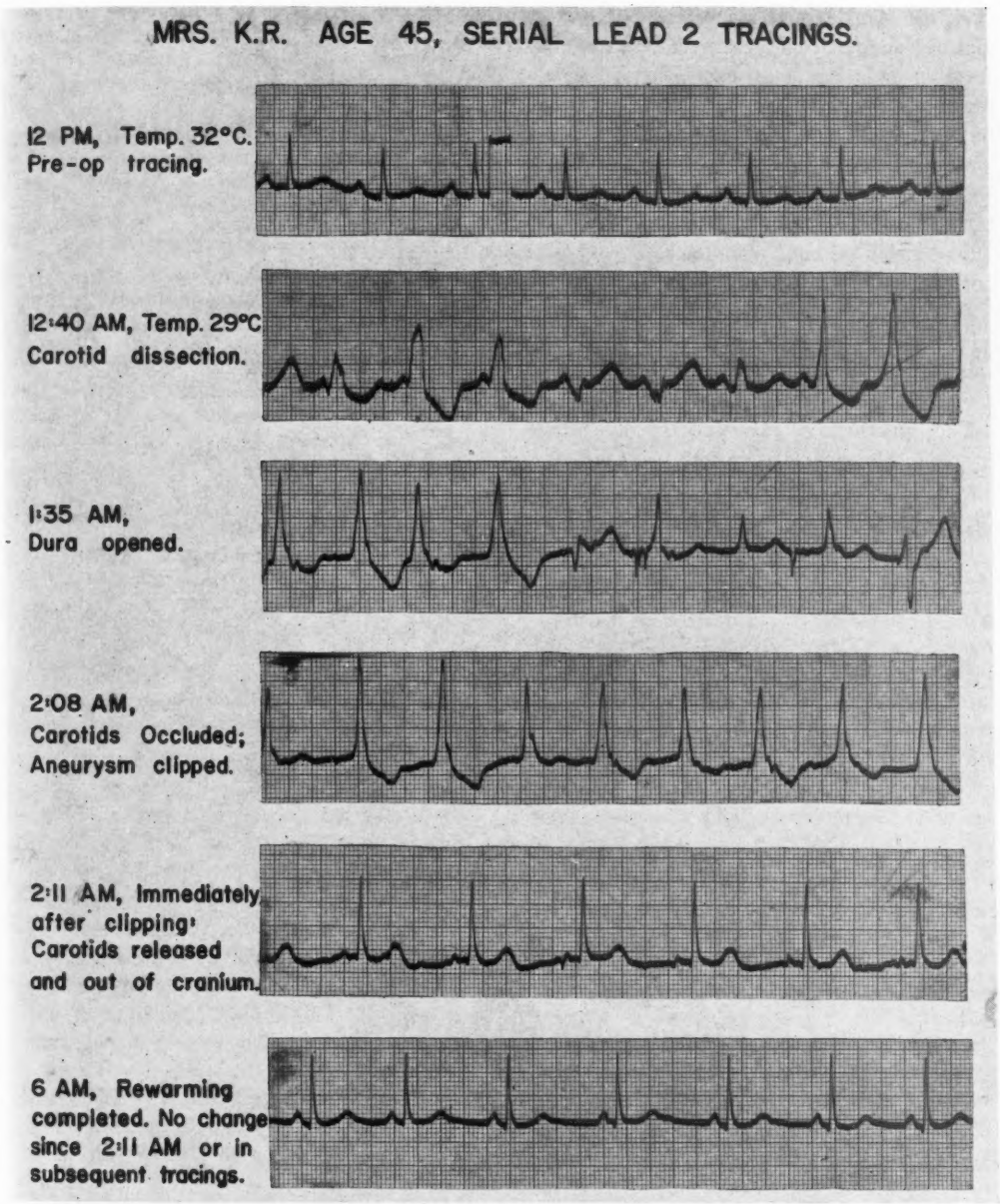
MRS. K.R. AGE 45, SERIAL LEAD 2 TRACINGS.
12 PM, Temp. 32°C. Pre-op tracing.
12:40 AM, Temp. 29°C Carotid dissection.
1:35 AM, Dura opened.
2:08 AM, Carotids Occluded; Aneurysm clipped.
2:11 AM, Immediately after clipping: Carotids released and out of cranium.
6 AM, Rewarming completed. No change since 2:11 AM or in subsequent tracings.

Figure 10

Mrs. K. R., age 45. Normal preoperative and postoperative electrocardiograms. Series of lead-II tracings showing changes (multifocal ventricular rhythm) occurring during operation with return to normal pattern immediately following ligation of aneurysm.

Conclusion

Fifteen cases of electrocardiographic abnormalities suggestive of recent myocardial infarction or ischemia in association with subarachnoid hemorrhage are described. Four patients with such abnormalities died and had a normal heart at autopsy. Of the 15 cases with abnormal electrocardiograms only 3 had symptoms of heart disease and 2 more had clinical hypertension without symptoms. The typical pattern was one with flat or negative T waves in lead I, aV_L, and V_4 to V_6, along with ischemic RS-T segment changes. These changes were, in a number of instances, suggestive of recent myocardial infarction.

The hypothesis is proposed that the cause for these abnormalities in the presence of a normal heart are lesions in the vicinity of area 13 on the orbital surface of the frontal lobe.

Acknowledgment

The authors gratefully acknowledge the cooperation of Dr. C. Drake and Dr. A. Douglas of the Neuro-Surgical Unit, Victoria Hospital, London, who carried out the neurologic investigation and treatment of all the cases used in this study.

Summario in Interlingua

Es describite 15 casos de anormalitates electrocardiographic que suggere le diagnose de recente infarcimento o ischemia myocardial in association con hemorrhagia subarachnoide. Quatro del patientes moriva, e le necropsia revelava un corde normal. Inter le 15 casos con electrocardiogrammas anormal, solmente 3 habeva symptomas de morbo cardiac, e 2 alteres habeva hypertension clinic sin symptomas. Le configuration typic habeva plan o negative undas T in le derivationes I, aV_L, eV_4 aV_6, in conjunction con alterationes ischemic in le segmento RS-T. In plure casos, iste alterationes suggereva un recente infarcimento myocardial.

Es proponite le hypothese que le causa de iste anormalitates in le presentia de un corde normal es lesiones in le vicinitate del area 13 al superficie orbital del lobo frontal.

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What can one hear with one's fingers? Vocal fremitus and a sharp second sound.—Sir William Osler. *Aphorisms From His Bedside Teachings and Writings.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 34.

Relatively Benign "Pure" Mitral Regurgitation of Rheumatic Origin

A Study of Seventy-Four Adult Patients

By SHEKHAR JHAVERI, M.D., GABOR CZONICZER, M.D., RAPHAEL B. REIDER, M.D., AND BENEDICT F. MASSELL, M.D.

HISTORICALLY there has been considerable diversity of opinion regarding the significance of the apical systolic murmur in relation to the diagnosis of mitral regurgitation and regarding the clinical course of this lesion. A general evolutionary pattern of thought concerning these problems can be traced over the past hundred years. Sir James Hope[1] in 1842 was the first to relate the systolic murmur to organic mitral regurgitation, and this view prevailed through the turn of the century. By 1906, however, the trend of opinion began to change as Graham Steell expressed his doubts that mitral regurgitation, indicated by an apical systolic murmur, could be due to disease of the mitral valve alone.[2] In 1913 Sir James MacKenzie,[3] impressed with the relatively uneventful course of this lesion, wrote that "symptoms produced by mitral incompetence are only of gravity when there is also muscle failure." Three years later he reinforced this opinion[4] by stating that he was dubious "whether mitral incompetence itself ever constitutes a serious embarrassment to the heart." The teaching that this lesion alone was never responsible for severe symptoms, congestive failure, or death unless complicated by other superimposed cardiac disease was carried on through the 1930's by Sir Thomas Lewis.[5] In 114 autopsied cases of rheumatic mitral valvular disease, Cabot[6] found only 17 instances of pure mitral regurgitation. He considered the latter lesion to be exceedingly rare and stated that "a clinical diagnosis of mitral regurgitation without stenosis is never justified."

A report by Sprague and White[7] in 1926 emphasized that an isolated apical systolic murmur should be accompanied by roentgenographic evidence of left ventricular enlargement before one could consider a diagnosis of mitral regurgitation. Even when this additional criterion was met, pure mitral regurgitation was thought to be most frequently a forerunner of mitral stenosis. It is of interest that Grant[8] failed even to mention pure mitral regurgitation among the cardiac valvular lesions classified in his extensive monograph of 1933.

Perhaps one of the earliest attempts to demonstrate the clinical significance of the apical systolic murmur was the investigation by Freeman and Levine[9] in 1933, in which 1,000 consecutive cases with this murmur alone were carefully and systematically studied. There were 804 murmurs of more than grade-II intensity that could almost invariably be correlated with organic valvular disease. Of the remaining 196 cases with grade-II murmurs or less all but 23 per cent were also associated with some organic lesion of the heart.

Certainly since the advent of cardiac surgery and modern diagnostic technics the existence of pure mitral regurgitation cannot be doubted. Current published opinions on the character and consequences of this lesion can be grouped into 3 main categories. One point of view, suggested by the observations of several investigators,[10–15] is that mitral regurgitation is a severe condition which may lead to cardiomegaly, arrhythmias, congestive failure, and death. Some of these investigators speak

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of functionally pure or predominant mitral regurgitation rather than pure mitral regurgitation, indicating the mixed nature of the lesion in many of their cases. A second opinion has been expressed by Wilson,[16] Magida,[17] Janton,[18] and their associates, who consider pure mitral regurgitation to be a relatively common and generally benign rheumatic valvular lesion. Bland and Jones,[19] in their analysis of the course of various rheumatic valvular lesions over a 20-year period, were also impressed with the benign character of mitral regurgitation. Some clinicians, such as Levine[20] and Friedberg,[21] have suggested a third concept, which recognizes the existence of 2 distinct groups of patients with mitral regurgitation: one, showing rapidly progressive and severe symptoms, whose prognosis is poor; and the other, showing a prolonged, stable and benign course, whose prognosis is good.

In view of the divergence of opinion the experience at the House of the Good Samaritan was analyzed with respect to (1) the long-term clinical course and the electrocardiographic and roentgenographic findings of adult clinic patients with pure mitral regurgitation of rheumatic origin and (2) the incidence of pure mitral regurgitation in fatal cases of rheumatic heart disease in adults.

Clinical Material and Methods

The source of material for the present study consisted of 1,843 patients who had been hospitalized at the House of the Good Samaritan. Of this total, 990 are patients who have attended the clinic within the past 2 years; the remaining 853 patients are all of those known to have died between 1917 and 1958.

Living Cases

Of the 990 patients observed in the clinic, 61 were selected for the present study on the basis of the following criteria:

1. Unequivocal signs of rheumatic heart disease during hospitalization at the House of the Good (with or without active rheumatic fever) recorded Samaritan.

2. An age of 17 years or more at the time of the most recent examination.

3. Documented auscultatory evidence of "pure" mitral regurgitation of at least 4 years' duration. Such evidence consists of (a) a systolic murmur of more than grade-II intensity (grading system of Levine and Harvey),[22] maximal at the apex and transmitted to the axilla or to the back of the chest, or both, (b) absence of any diastolic or other significant systolic murmur, (c) a normal, diminished, or completely masked mitral first sound. Six patients with apical systolic murmurs of only grade-II intensity were included because their murmurs were of such duration, quality, and transmission as to be considered significant.

4. No evidence for any other pathologic condition to account for the murmur, such as fever, anemia, hyperthyroidism, hypertension, rheumatic activity, or nonrheumatic myocardial disease.

Five patients satisfying the above criteria were considered separately because they also had a history of subacute bacterial endocarditis. The remaining 56 patients had uncomplicated "pure" mitral regurgitation. Figure 1 illustrates schematically the source and selection of clinical material and gives the actual numbers of cases in each group as delineated by the criteria enumerated above.

The age of 17 years was chosen as the lower limit for inclusion of patients in this series because several previous studies,[23–25] from this hospital also employed the age of 17 as the dividing line between the childhood and adult patterns of rheumatic heart disease. The minimum period of 4 years for duration of an isolated systolic murmur was chosen in order to eliminate patients with labile auscultatory findings often observed following rheumatic activity.

All patients studied in this series have been carefully followed in the clinics of the House of the Good Samaritan for the most part at 6-month to 1-year intervals. Their medical records were reviewed in detail to assess their clinical course from first admission to the present time. Each patient was examined by at least 2 of the authors at a recent clinic visit to confirm the diagnosis of "pure" mitral regurgitation.

Several 12-lead electrocardiograms taken over the follow-up period were available on each patient. The most recent tracing, obtained in every case within the past year, was utilized for analysis. All these tracings were taken on the Sanborn Viso-Cardiette machine. Every electrocardiogram was carefully reviewed by 2 or more of the authors and was evaluated according to the recommendations of the Committee on Electrocardiography of the American Heart Association[26] and according to the normal standards described by Kossmann.[27] For the interpretation of left and right ventricular hypertrophy the voltage criteria of Sokolow and Lyon[28, 29] were employed. It was thought that, if these voltage requirements were fulfilled, while they admittedly are not infallible, any errors

would tend to include false positives rather than to exclude certain cases in which there might be true hypertrophy.

Roentgenographic examinations were obtained within the past 6 months on 55 patients. The remaining 6 patients had moved from the area, failed to keep their appointments, or were deferred from this part of the study because of pregnancy. These examinations included standard posteroanterior and oblique films, fluoroscopy, and barium swallow. Roentgenographic abnormalities were graded on a 1-to-4 scale to signify degrees of chamber enlargement ranging from minimal to massive. During fluoroscopy particular attention was directed to the movements of the left atrium in order to detect even a slight degree of systolic expansion of this chamber.

Fatal Cases

In order to minimize any bias that might arise from the study of living cases only, the records of all House of the Good Samaritan patients who died from the beginning of 1917 to the end of 1958 were also analyzed. This analysis, which involved a careful review of 853 fatalities, provided data on the incidence of "pure" mitral regurgitation and its frequency as a cause of death in a parallel group of individuals who died with rheumatic heart disease. The same criteria for inclusion under "pure" mitral regurgitation were applied to the deceased cases as to the living and, as figure 2 shows, a similar method of selection was used.

Results

In the living group 61 (20.3 per cent) of 300 patients with rheumatic heart disease who were 17 years of age or older fulfilled the given criteria for "pure" mitral regurgitation (fig. 1). Five of these were considered separately because they also had a history of subacute bacterial endocarditis, thus leaving a total of 56 cases (18.6 per cent) with the uncomplicated lesion. Hereafter, unless otherwise indicated, all data relate to these 56 patients with uncomplicated mitral regurgitation.

The range in age was 17 to 55 with both a mean and a median age of 30 years. The sex distribution of this group was 46 women (82 per cent) and 10 men (18 per cent). These figures are not intended to show that mitral regurgitation is overwhelmingly predominant in women. They may to some extent reflect the fact that beds at the House of the Good Samaritan were not always equally available for both sexes. The period of observation of

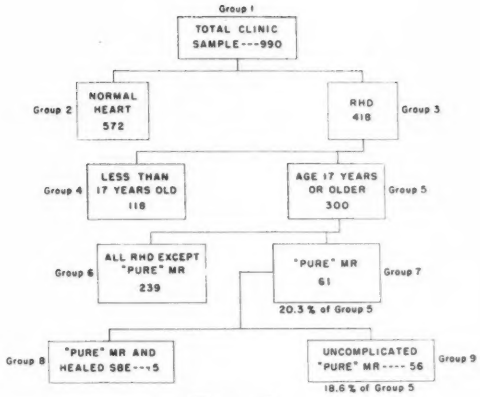

Figure 1

Analysis of sample of clinic patients showing source of cases of "pure" mitral regurgitation.

these cases, which also corresponds with the time elapsed since the systolic murmur was first recorded, ranges from 4 to 37 years with a mean of 18 and a median of 19 years.

Clinical Findings

The distribution of patients according to intensity of systolic murmurs was as follows: 6 patients had a grade-IV murmur, 5 had a grade-III plus, 16 a grade-III, 23 a grade-II plus, and 6 had a grade-II murmur with such quality, duration, and transmission that it was considered significant. None of the murmurs was accompanied by a precordial thrill. In no patient did physical examination reveal an abnormal cardiac impulse characteristic of left or right ventricular hypertrophy nor was there any instance of atrial fibrillation or other disturbances of rhythm. Pain in the legs, undue fatigue, and palpitation were specifically denied by every patient. No one in the entire series had any sign or symptom of congestive heart failure at any time during the period of observation, and none had ever required cardiac medication.

Electrocardiographic Data

Table 1 summarizes the electrocardiographic findings in the series of 56 patients with uncomplicated "pure" mitral regurgitation. It is of particular interest that 77 per cent of these patients had completely normal tracings. There were 3 patients (5 per cent) whose only

Table 1

*Electrocardiographic Data in Fifty-six Cases of "Pure" Mitral Regurgitation**

Electrocardiographic diagnosis	Number of cases
No abnormalities	43 (77%)
One or more abnormalities	13 (23%)
Atrial fibrillation	0
Other arrhythmias (excluding sinus arrhythmia)	0
P mitrale	3 (5%)
Abnormal axis deviation	0
Bundle-branch block	1 (2%)
Right ventricular hypertrophy	0
Left ventricular hypertrophy	9 (16%)

*Exclusive of 5 cases with previous bacterial endocarditis.

Table 2

Electrocardiographic Criteria of Left Ventricular Hypertrophy in 9 Cases

Criteria[28]	Instances		Cases
$Rav_L > 11$ mm.	0		
$Rav_F > 20$ mm.	2		
Rv_5 or $Rv_6 > 26$ mm.	2		
$Sv_1 + Rv_6$ or $Rv_6 > 35$ mm.	9	LVH by voltage criteria alone	7
Intrinsicoid deflection 0.05 sec. or more	1	LVH by intrinsicoid deflection alone	1
ST-T changes	1	LVH by voltage and ST-T changes	1
		Total	9

electrocardiographic abnormality was the presence of wide, notched P waves (so-called "P-mitrale"), and 1 patient showed complete right bundle-branch block pattern in an otherwise normal tracing.

The remaining electrocardiographic abnormalities in 9 cases (16 per cent) reflected left ventricular hypertrophy. An analysis of these findings according to the various criteria fulfilled, either singly or in combination, is presented in table 2. It is noteworthy that only 1 patient had ST-T changes in addition to satisfying the voltage requirements for left ventricular hypertrophy. Seven patients were diagnosed as having left ventricular hypertrophy on the basis of voltage alone, and an additional case showed only a delayed intrinsicoid deflection, the latter considered by some to be the least reliable of the listed criteria.[30]

Roentgenographic Data

Of the 50 complete roentgenographic examinations performed, 40 (80 per cent) were entirely within normal limits (table 3). The remaining 10 cases showed abnormalities classified as minimal or moderate (grade I or II on a scale of 4), and in no instance was there marked or massive chamber enlargement.

Correlation of Electrocardiographic and Roentgenographic Data

As shown in table 4, only 2 patients (4 per cent) of the 50 studied by both technics showed electrocardiographic evidence of left ventricular hypertrophy and also roentgenographic evidence of left ventricular enlargement. There were 7 cases (14 per cent) in which the only manifestation of the left ventricular involvement was electrocardiographic evidence of hypertrophy. Of special interest were 6 patients (12 per cent) with radiologic findings of right ventricular enlargement in the absence of signs of left ventricular enlargement. Not 1 of these 6 showed any electrocardiographic abnormality of the corresponding chamber, but 2 of them did have left ventricular hypertrophy. Both technics failed to show any abnormality of either ventricle in 37 cases (74 per cent) and of the left ventricle in 41 cases (82 per cent).

Correlation of Electrocardiographic and Roentgenographic Findings with Gradation of Murmurs

The distribution of cases according to gradation of the systolic murmur and the corresponding incidence of electrocardiographic and roentgenographic abnormalities of all types in each group are presented in section A of table 5. A cursory inspection of these data suggests that the likelihood of finding some objective abnormality roughly parallels the intensity of the murmur, but the numbers of patients in each of the groups are so small that the apparent correlation cannot be readily checked by statistical analysis.

Therefore, in section B of table 5 the cases have been retabulated so that there are 2 groups of as nearly equal size as possible, one

Table 3

*Roentgenographic Data in Fifty Cases of "Pure" Mitral Regurgitation**

X-ray diagnosis	Number of cases			
No abnormalities	40 (80%)			
One or more abnormalities	10 (20%)			
	Minimal	Moderate	Marked	Massive
Left atrial enlargement	4	5	0	0
Left ventricular enlargement	1	1	0	0
Systolic pulsation of left atrium	0	0	0	0
Right ventricular enlargement	2	4	0	0
Enlargement of pulmonary artery	0	0	0	0
Increased pulmonary vascular markings	0	0	0	0
Calcification of mitral valve	0	0	0	0

*Exclusive of 5 cases with previous bacterial endocarditis.

group being composed of 27 patients with systolic murmurs of grade III or more intensity and the other of 29 patients with murmurs of grade II plus or less intensity. Of the group with the louder murmurs, 33 per cent had some electrocardiographic abnormality, and 29 per cent had some roentgenographic abnormality; for the group with the less intense murmurs these figures were 14 per cent and 12 per cent respectively. Statistical analysis of the results reveals a P value of between 0.1 and 0.2 for the electrocardiographic data and between 0.2 and 0.3 for the roentgenographic data. Since these probabilities are not within the accepted limits of statistical significance, it must be concluded that the correlation of incidence of electrocardiographic and roentgenographic abnormalities with intensity of the murmurs may be suggestive but is not definite.

Time Elapsed Since Appearance of Systolic Murmur Compared with Electrocardiographic and Roentgenographic Findings

No significant relationship could be demonstrated between the period of observation (i.e., the time elapsed since the murmur of mitral regurgitation was first heard) and the incidence of electrocardiographic or roentgenographic abnormalities, or both.

Table 4

*Correlation of Electrocardiographic and Roentgenographic Signs of Ventricular Size in Fifty Cases**

Electrocardiographic and x-ray findings	Number of cases		
	Left ventricle	Right ventricle	Both ventricles
Hypertrophy by electrocardiogram alone	7	0	0
Enlargement by x-ray alone	0	6†	0
Hypertrophy by electrocardiogram *and* enlargement by x-ray	2	0	0
No hypertrophy by electrocardiogram and no enlargement by x-ray	41	44	37

*Exclusive of 5 cases with previous bacterial endocarditis.

†Two of these 6 cases with right ventricular enlargement by x-ray also had left ventricular hypertrophy by electrocardiogram. All 6 patients had minimal to moderate left atrial enlargement.

Data on Patients with History of Subacute Bacterial Endocarditis

In the review of the clinic records, 5 patients were encountered who met all the criteria for inclusion in the series except that at some time during the follow-up period each had had subacute bacterial endocarditis. Because this disease may superimpose additional permanent damage on a heart already scarred by the rheumatic process, these cases were considered separately even though no new murmurs appeared subsequent to the endocarditis. The data summarized in table 6 suggest that such patients constitute a group with more severe heart disease. All had some abnormality by electrocardiographic or roentgenographic examination, and all had a systolic murmur of grade-III intensity or louder. In fact 3 of the 5 patients had a grade-IV murmur.

Analysis of Fatal Cases

Over the 42-year period from 1917 through 1958, 853 deaths from any cause among House of the Good Samaritan patients were recorded during hospitalization or during the follow-up period. The records of these patients were analyzed in a manner similar to that used for the living series. Thus, all individuals classified under "pure" mitral regurgitation were 17 years of age or older at the time of death,

Table 5

Correlation of Electrocardiographic and Roentgenographic Findings with Gradation of Systolic Murmurs

Grade of murmur	Number of cases	A Electrocardiographic findings		Roentgenographic findings		
		Normal	Abnormal	Normal	Abnormal	No data
IV	6	3	3 (50%)	1	4 (80%)	1
III+	5	3	2 (40%)	2	2 (50%)	1
III	16	12	4 (25%)	14	1 (7%)	1
II+	23	19	4 (17%)	17	3 (15%)	3
II	6	6	0 (0%)	6	0 (0%)	0
Total	56	43 (77%)	13 (23%)	40 (80%)	10 (20%)	6
		B				
Grade III and above	27	18	9	17	7	3
Per cent of group		(67%)	(33%)	(71%)	(29%)	
Grade II+ and below	29	25	4	23	3	3
Per cent of group		(86%)	(14%)	(88%)	(12%)	

all had a definite history of rheumatic fever, and all had a significant apical systolic murmur documented over a period of at least 4 years' duration. This analysis is schematically illustrated in figure 2, which shows that 13 cases met the criteria for "pure" mitral regurgitation. Of these, 6 died of accidents or causes unrelated to rheumatic heart disease. Of the remaining 7 cases in the group, 1 died of subacute bacterial endocarditis, 3 of definite recurrent rheumatic fever accompanied by the development of new murmurs, 2 of carditis, which was presumably a manifestation of recurrent rheumatic activity, and 1 of severe rheumatic heart disease 4 years after a plastic prosthesis was inserted within the mitral ring. Thus, only 1.9 per cent of 372 deaths occurring after the age of 17 in patients with rheumatic heart disease could be related directly or indirectly to "pure" mitral regurgitation. This low number of deaths related to "pure" mitral regurgitation is particularly striking when compared to the 20.3 per cent incidence of this lesion in the parallel group of living patients (fig. 1).

Discussion

From the foregoing data it would appear that patients fulfilling the criteria for "pure" mitral regurgitation, as defined in this report, have a relatively benign type of rheumatic heart disease. Although this conclusion seems to differ from the conclusions of many other investigators, the apparent disparity can be explained largely on the basis of the criteria used for selection of cases.

Of 30 cases of mitral regurgitation reported by Brigden and Leatham,[31] 15 had palpitation, 6 had heart failure, 7 had bacterial endocarditis, and 1 had dyspnea as presenting symptoms. All of the patients showed cardiac enlargement by roentgenographic examination, and 21 had one or more abnormal electrocardiographic findings. Nine of the patients died. It is apparent that the cases reported by Brigden and Leatham had more severe heart disease than those observed by us. However, these investigators included only patients with grade-IV systolic murmurs. Furthermore, patients with a history of bacterial endocarditis were not considered separately, and the mean age of their group was 2 decades beyond that of the present series. In a group of patients of this age the possible role of additional factors such as arteriosclerosis must also be considered.

Other studies have been limited to cases that came to autopsy or to patients whose symptoms were disabling enough to warrant

cardiac catheterization or surgery.[10–15] In one such study by Ross and his associates[13] pure mitral regurgitation was diagnosed by left heart catheterization in 23 patients. The diagnosis was proved by autopsy in 3 of these cases and by operation in 5. Six of the 23 patients had diastolic murmurs. Bentivoglio and his group,[14] who recently reported on the incidence of electrocardiographic abnormalities in 65 cases of "dynamically significant" mitral regurgitation, selected only patients who underwent surgery (except for 1 patient who died preoperatively). Many of these patients had diastolic murmurs. In 2 other reports,[12, 15] which were also concerned only with patients subjected to mitral valve surgery, the patients could be considered to be cases of predominant rather than pure mitral regurgitation. Furthermore, a diastolic murmur in addition to a systolic murmur was either mentioned or implied in most instances. In all the studies cited here, there was a high incidence of severe cardiac symptoms and of electrocardiographic and roentgenographic abnormalities. These findings are not surprising in view of the way the cases were selected.

In contrast, the figures of Wilson and her associates[16, 17] seem to characterize mitral regurgitation as a common and generally benign lesion. It is not possible to compare their data with ours, however, since the apical systolic murmur of mitral regurgitation had "regressed" in two thirds of their patients and presumably, had disappeared in many instances. Such patients, even though they may have had carditis in childhood, would not have been classified by us as having mitral regurgitation during adult life.

Thus, it becomes apparent that the particular group of patients considered in the present communication, in so far as its clinical picture and course are concerned, has received only casual attention in the recent literature.

There can be little doubt that the isolated apical systolic murmur observed in our living patients reflects actual rheumatic valvular disease, since in all cases it originated with an attack of active rheumatic fever. Although precise hemodynamic data on the degree of mitral regurgitation in each case would be of interest, it was considered that the discomfort and risk did not justify left cardiac puncture in individuals who had been completely asymptomatic.

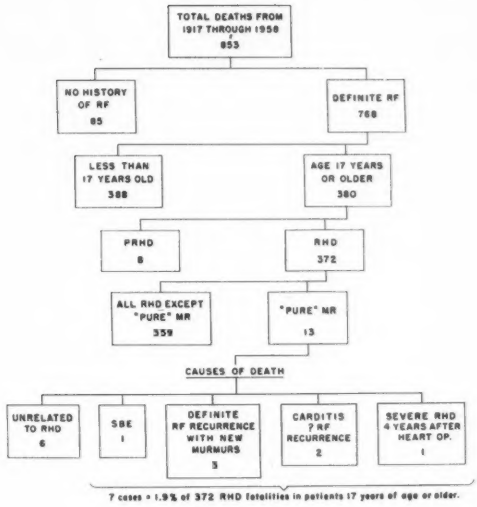

Figure 2

Analysis of deaths from 1917 through 1958 showing source of fatal cases of "pure" mitral regurgitation. The term PRHD applies to patients who have had rheumatic fever without apparent heart involvement.

It is evident from the data of others that there does exist a group of progressively severe and sometimes fatal cases of pure mitral regurgitation, which contrasts strikingly with our group of living cases of relatively benign mitral regurgitation. Although this conclusion may seem to suggest the existence of only 2 categories of mitral regurgitation, one mild and the other severe, it is unlikely that all patients with pure mitral regurgitation can be placed in one of these 2 distinct groups. Instead, patients with mitral regurgitation probably fall into a broad spectrum which ranges from mild and benign at one end to severe and progressive at the other end.

The observation of a diastolic murmur in addition to a systolic murmur in patients with functionally pure mitral regurgitation,[13, 14, 32] is of considerable interest. Since all of the individuals with this finding had advanced heart disease, it may well be that the presence of a diastolic murmur in a patient with pure mitral

Table 6

Summary of Electrocardiographic and Roentgenographic Data in Five Cases of "Pure" Mitral Regurgitation with a History of Subacute Bacterial Endocarditis

Electrocardiographic findings	Number of cases
Left ventricular hypertrophy	4
No abnormalities	1*
X-ray findings	
Left atrial enlargement	2
Left ventricular enlargement	3
Right ventricular enlargement	3
Systolic pulsation of left atrium	2
No abnormalities	1*

*The patient with no electrocardiographic abnormalities is not the same case as the patient with no x-ray abnormalities.

regurgitation assigns the patient to the severe portion of the spectrum. Such cases were automatically excluded from the present series by our criteria.

The intensity of the systolic murmur in pure mitral regurgitation may possibly also be some measure of severity. Thus, many or all of the cases with severe mitral regurgitation reported by Movitt,[10] Ross,[13] Bentivoglio,[14] Brigden[31] and their associates had grade-IV or "loud" systolic murmurs. In contrast, all but 6 of our 56 living patients with uncomplicated "pure" mitral regurgitation had systolic murmurs that were of less than grade-IV intensity. Furthermore, a tabulation of these 56 patients according to the intensity of their murmurs shows a rough parallelism between the intensity of the systolic murmur and the incidence of electrocardiographic and roentgenographic abnormalities. Although this correlation cannot be shown to be statistically significant, the findings are consistent with the concept that the more severe the mitral regurgitation the louder the systolic murmur is likely to be.

Since all of the 56 patients were asymptomatic and since the electrocardiographic and roentgenographic abnormalities were comparatively mild and their over-all incidence low, it seems reasonable to conclude that the living patients in the present series can be assigned to various positions within the mild and benign portion of the severity spectrum.

A critical appraisal of the small number of patients in the present series with "pure" mitral regurgitation who succumbed to their disease reveals that the majority of deaths could be attributed to the subsequent development of recurrent rheumatic carditis or of bacterial endocarditis. Thus, it appears that one of these complications rather than "pure" mitral regurgitation alone is the usual cause of progressive cardiac damage in patients who enter adult life with a mild lesion. The presence of electrocardiographic or roentgenographic abnormalities in all 5 patients in this study who had a history of bacterial endocarditis also supports this thesis.

The presence of right ventricular enlargement by x-ray in 6 patients requires brief comment. This so-called paradox of right ventricular enlargement in mitral regurgitation has been documented in 4 severe cases by Bentivoglio and his associates.[33] In these cases there was right ventricular hypertrophy by electrocardiogram as well as right ventricular enlargement by x-ray. Although right ventricular hypertrophy by electrocardiogram was absent in all our patients, the roentgenographic findings suggest that the paradox of right ventricular enlargement may occur even in benign "pure" mitral regurgitation.

Summary and Conclusions

The records of 990 living patients and 853 deceased patients observed at the House of the Good Samaritan were analyzed with respect to the incidence and clinical course of "pure" mitral regurgitation. A total of 74 patients, 61 from the living group and 13 from the deceased group, met the criteria specified for this lesion.

The 61 patients in the living group constituted 20.3 per cent of 300 living patients with rheumatic heart disease who were 17 years of age or older. Of the 13 fatal cases, 6 died of causes unrelated to rheumatic heart disease. The remaining 7 cases, in which death could be related directly or indirectly to "pure" mitral regurgitation, constituted only 1.9 per cent of 372 fatalities occurring in patients with rheumatic heart disease who had passed their seventeenth birthday.

Of the 61 living patients with "pure" mitral regurgitation, 5 gave a history of subacute bacterial endocarditis. The remaining 56 patients were cases of uncomplicated "pure" mitral regurgitation.

The group of 56 cases of uncomplicated "pure" mitral regurgitation illustrate the benign character of this lesion. All of these patients have been asymptomatic, all have enjoyed fully normal, unrestricted activity, and none has shown any evidence of congestive failure or of any arrhythmia over the entire follow-up period ranging from 4 to 37 years, with a mean of 18 and a median of 19 years.

In the series of uncomplicated cases, 77 per cent had normal electrocardiograms and 80 per cent of those studied by x-ray had normal roentgenographic findings. Of particular interest was the notably low incidence of left ventricular hypertrophy by electrocardiogram (16 per cent) and the absence of marked enlargement of any cardiac chamber by x-ray.

All 5 patients with "pure" mitral regurgitation and a history of subacute bacterial endocarditis had electrocardiographic or roentgenographic abnormalities.

Of the 7 fatal cases of "pure" mitral regurgitation in which death was related to the presence of rheumatic heart disease, 6 either had evidence of recurrent rheumatic activity or had documented bacterial endocarditis.

It is concluded that, in general, an individual, age 17 years or older, whose only auscultatory sign of rheumatic heart disease has been a significant apical systolic murmur for a period of 4 years or longer can be classified as having a benign type of mitral regurgitation. Such a patient, barring recurrent rheumatic fever and bacterial endocarditis, has a good prognosis.

Acknowledgment

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Summario in Interlingua

Le dossiers de 990 patientes vive e de 853 patientes morte, vidite al Domo del Bon Samaritano a Boston, esseva analysate con respecto al incidentia e al curso clinic de "pur" regurgitation mitral. Un total de 74 patientes, 61 vive e 13 morte, satisfaceva le criterios establite pro iste lesion.

Le 61 patientes vive representava 20,3 pro cento de un gruppo de 300 patientes vive con morbo cardiac rheumatic qui habeva 17 annos de etate o plus. Ex le 13 patientes morte, 6 moriva ab causas non relationate a morbo cardiac rheumatic. Le remanente 7 patientes in qui le morte poteva esser relationate directe- o indirectemente con lor regurgitation mitral "pur" constitueva solmente 1,9 pro cento del 372 mortes occurrente in patientes con rheumatic morbo cardiac de etates de plus que 17 annos.

Inter le 61 patientes vive con "pur" regurgitation mitral, 5 habeva un historia de subacute endocarditis bacterial. In le remanente 56, il se tractava de casos de non-complicate regurgitation mitral "pur."

Iste gruppo de 56 casos de non-complicate regurgitation mitral "pur" illustra le benigne character de iste lesion. Omne iste patientes ha essite asymptomatic, ha gaudite de completemente normal e non restringite activitate, e ha nunquam exhibite signos de disfallimento congestive o del un o del altere arrhythmia durante le integre periodo de observation, i.e. depost inter 4 e 37 annos, con un duration medie de 18 e median de 19 annos.

In le serie del non-complicate casos, 77 pro cento habeva electrocardiogrammas normal, e le constatationes roentgenoscopic esseva normal in 80 pro cento del casos assi examinate. De interesse particular es le notabilemente basse incidentia de hypertrophia sinistro-ventricular in le electrocardiogrammas (amontante a solmente 16 pro cento) e le absentia de marcate grados de allargamento de un del cameras secundo le roentgenogramma.

Omne le 5 patientes con "pur" regurgitation mitral e un historia de subacute endocarditis bacterial manifestava anormalitates electrocardiographic o roentgenographic.

Inter le 7 casos mortal de "pur" regurgitation mitral in que le morte esseva relationate al presentia de rheumatic morbo cardiac, 6 habeva (1) evidentia de recurrente activitate rheumatic o (2) un documentate endocarditis bacterial.

Le conclusion es que, a generalmente parlar, un subjecto de 17 annos de etate o plus in qui le sol signo auscultatori de rheumatic morbo cardiac es un significative murmure systolic apical depost 4 annos o plus pote esser classificate inter le casos de un benigne typo de regurgitation mitral. Un tal patiente—in le absentia de recurrente febre rheumatic e de endocarditis bacterial—ha un bon prognose.

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The Electrocardiogram in Children with Ventricular Septal Defect and Severe Pulmonary Hypertension

Correlation with Response of Pulmonary Arterial Pressure to Surgical Repair

By JAMES W. DUSHANE, M.D., WILLIAM H. WEIDMAN, M.D., ROBERT O. BRANDENBURG, M.D., AND JOHN W. KIRKLIN, M.D.

SUCCESS in the surgical treatment of children who have large ventricular septal defects is dependent in part on the proper selection of patients for operation. The patients most deserving of such correction are those who have severe pulmonary hypertension, and it is in these that the decision to offer surgical intervention may present the greatest problems.

The factors influencing the increase in pulmonary arterial pressure deserve critical analysis. Elevated pulmonary arterial pressure in patients with large ventricular septal defects is, to a great extent, the result of 2 factors, namely increased pulmonary blood flow or increased pulmonary vascular resistance; both factors are present in some instances. In those patients without pulmonary vascular disease but with a high pulmonary blood flow in relationship to systemic blood flow and with only slightly increased pulmonary vascular resistance, the pulmonary arterial pressure may be equal or nearly equal to the systemic pressure. In those who have complicating pulmonary vascular disease in whom the pulmonary resistance is increased and the pulmonary blood flow is not increased in relationship to systemic flow, the pulmonary and systemic pressures may be equal or nearly equal.

If the increased pulmonary arterial pressure is primarily the result of increased pulmonary blood flow from a left-to-right shunt, surgical closure of the defect will result in a decrease in pulmonary arterial pressure. If the increased pulmonary pressure is secondary to obliterative changes in the pulmonary vasculature, with the pulmonary blood flow only equal to or less than the systemic flow, the shunt being predominantly from right to left, then closure of the defect will not result in an immediate decrease in pulmonary arterial pressure. In the latter situation, operative repair of the defect is thought to be detrimental to the patient and probably should be avoided.[1]

The important consideration in the choice of patients to whom surgical treatment should be offered is the relationship between pulmonary and systemic blood flows, whether the shunt is predominantly from left to right or right to left, rather than the height of the pulmonary arterial pressure by itself. The present study is concerned with the evaluation of this relationship between pulmonary and systemic blood flows from electrocardiographic data.

When the dominant shunt is from left to right and the pulmonary blood flow is greater than the systemic flow, the extra volume of shunted blood returns to the left side of the heart, resulting in an increase in the work of the left ventricle. When the shunts are balanced or dominantly from right to left, there is no increase in pulmonary blood flow or in the work of the left ventricle. The electrocardiogram, when properly interpreted, reflects increased work by the left ventricle. Thus, electrocardiographic evidence of left ventricular overloading in patients with isolated ventricular septal defect who do not have mitral or aortic valvular disease, coarctation of the aorta, or systemic hypertension should indicate

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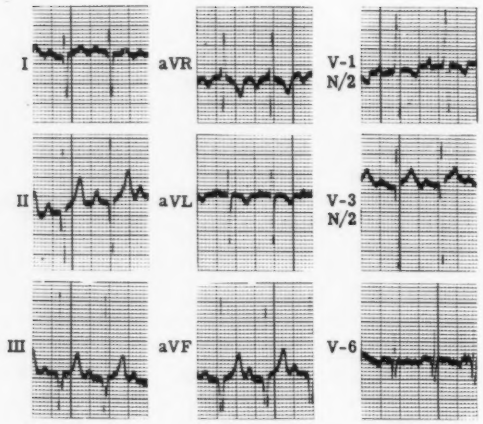

Figure 1

Electrocardiogram in a 2-year-old boy (see table). Note evidence of right ventricular hypertrophy. Left ventricular overwork is manifested by peaked symmetric T waves in leads II, III, and aV_F (criterion 1).

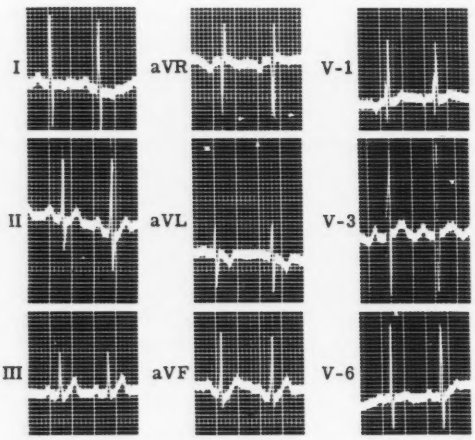

Figure 2

Electrocardiogram in a 4-month-old girl (see table). Note evidence of right ventricular hypertrophy. Left ventricular overwork is manifested by an axis deviation of mean QRS vectors of +60 degrees in the frontal plane (criterion 5).

a left-to-right shunt and an increased pulmonary blood flow regardless of the level of pulmonary arterial pressure.

Methods

Electrocardiograms from 100 children with ventricular septal defects whose pulmonary arterial pressures were 80 to 100 per cent of systemic pressures and who had been operated on were mixed with 25 electrocardiograms from children without demonstrable cardiac disease and with 17 electrocardiograms from children who had ventricular septal defects and pulmonary hypertension whose shunts were proved to be dominantly from right to left. These tracings were analyzed by the first 3 authors independently, after all identifying information had been removed except the age of the child, in an effort to determine electrocardiographic evidence of left ventricular overwork.

Specific standards for electrocardiographic signs of an overworking left ventricle in infants and children have not been established, particularly when coexistent patterns of right ventricular hypertrophy are present. A number of features of the scalar electrocardiogram suggest left ventricular overwork, but many of these are difficult to define clearly or do not lend themselves to analysis by numerical limits or ratios. Seven criteria for left ventricular overwork were chosen arbitrarily for this study, since these criteria can be defined clearly and applied by any investigator. It is emphasized that these are not absolute and infallible. Some normal infants and children may have some of these features, although such instances are rare.

Left ventricular overwork was considered to exist if one or more of these 7 electrocardiographic features were present:

1. Peaked, symmetric, or nearly symmetric T waves in leads reflecting left ventricular potential in children at any age (lead V_6, or leads II, III, and aV_F)[2, 3] (fig. 1).

2. Q waves greater than 0.4 mv. (4.0 mm.) in precordial lead V_6 in patients more than 3 years of age.

3. R waves greater than 2.5 mv. (25 mm.) in precordial lead V_6 in children at any age.

4. S waves greater than the R waves in lead V_{3R} or V_1 in patients less than 2 years of age, or S waves in lead V_1 greater than 2.5 mv. (25 mm.) at any age.

5. Axis of mean QRS vectors in the frontal plane of +60 degrees or less in infants less than 3 years of age (fig. 2).

6. Counterclockwise QRS loops in the frontal plane, as determined by vectorial analysis of the scalar electrocardiograms, in infants less than 3 years of age (fig. 3).

7. Combination of criteria 5 and 6 in children less than 6 years of age (fig. 3).

The criteria (1, 5, 6, and 7) that are not mathematically definable are illustrated in the afore-mentioned 3 figures. The pulmonary arterial and systemic pressures in the 3 patients from whom these

electrocardiograms were obtained are summarized in table 1.

Pulmonary arterial and systemic arterial pressures had been measured in the operating room immediately before and after surgical repair of the defects. The response of the pressures to closure of the defects was compared with the electrocardiographic evidence of left ventricular overwork in each case. A decrease in the pulmonary arterial systolic pressure to a level of 70 per cent or less of systemic arterial systolic pressure was considered to be significant evidence of pre-existing increased pulmonary flow. A decrease to 90 per cent was considered insignificant. A decrease to 75 or 80 per cent of the systemic pressure was studied carefully and was considered to be significant if the pulmonary arterial pressure was actually equal to (100 per cent of) the systemic pressure before operation in that particular patient, thus indicating a pulmonary flow a little in excess of the systemic flow.

Results

All the electrocardiograms from the 25 children without demonstrable cardiac disease were considered to be normal by the authors.

All the electrocardiograms from the 17 patients who had obvious, predominant right-to-left shunts and cyanosis were considered to show evidence of increased pressure in the right ventricle, but none was considered to demonstrate overwork of the left ventricle.

The electrocardiograms from 90 of the 100 patients with ventricular septal defects and pulmonary hypertension who had surgical closure of the defects showed evidence of left ventricular overwork; all of these 100 patients also had electrocardiographic evidence of increased right ventricular pressure. The pulmonary arterial systolic pressure in 89 of these 90 patients decreased after repair, giving a correlation of 99 per cent and proving a pre-existing pulmonary blood flow. In these 89 cases, the pulmonary arterial pressure in 1 decreased to 75 per cent of the systemic pressure, but the preoperative pulmonary pressure had been 100 per cent of the systemic pressure in this instance; the pulmonary arterial pressure decreased to 70 per cent in 2 cases, and in the remainder it decreased to a level of 60 per cent or less of the systemic pressure.

The remaining 10 of the 100 patients who had ventricular septal defects and pulmonary hypertension were considered not to exhibit any of the electrocardiographic criteria for left ventricular overwork already listed. The pulmonary arterial pressure did not decrease significantly in 5 of these after repair, indicating the absence of a preexisting increased pulmonary blood flow. Of the remaining 5 patients, 1 had a postoperative pulmonary pressure that was 75 per cent of the systemic pressure, but the preoperative pulmonary pressure had been 80 per cent of the systemic pressure, indicating no significant increase in pulmonary flow; 2 patients had a postoperative pulmonary systolic pressure of 75 per cent of the systemic pressure as compared with a preoperative level of 100 per cent, thus indicating a slight increase in pulmonary blood flow; the remaining 2 patients experienced a significant decrease in pulmonary arterial pressure, the final level being 70 per cent of the systemic pressure or less.

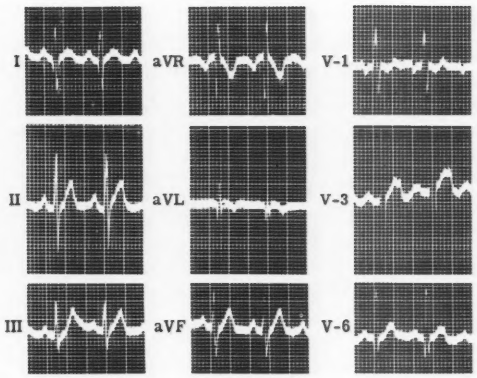

Figure 3

Electrocardiogram in a 2-year-old boy (see table). Note evidence of right ventricular hypertrophy. Left ventricular overwork is manifested by a counterclockwise loop of QRS in the frontal plane as determined by vectorial analysis of the scalar electrocardiogram (criterion 6).

Discussion

If a ventricular septal defect is large, there is little resistance to the flow of blood across the defect. The relationship of pulmonary arterial resistance and systemic arterial resistance is, therefore, a dominant factor in determining the relative amounts of blood flowing

Table 1

Response of Pressures in the Three Patients Whose Electrocardiograms Are Illustrated in Figures 1, 2, and 3*

Electrocardiogram pictured in:	Relationship to repair of septal defect	Arterial pressures, (mm. Hg) Pulmonary	Systemic	Pulmonary pressure, per cent of systemic pressure
Figure 1	Before	62/32	65/35	95
	After	55/9	112/48	49
Figure 2	Before	64/12	75/37	85
	After	37/12	70/27	53
Figure 3	Before	68/20	58/46	117
	After	48/20	76/38	63

*Recorded in operating room.

from the ventricles into the pulmonary artery and aorta. In the absence of obstructive disease in the pulmonary vasculature, the pulmonary resistance is less than the systemic resistance and the pulmonary blood flow is greater than the systemic flow. The hemodynamic continuity of the left ventricle and the pulmonary artery is reflected by the presence of systemic, or near systemic, pressure in the pulmonary artery. When severe pulmonary vascular obstructive changes occur, the pulmonary resistance may approach or equal the systemic resistance, with resultant equalization of pulmonary and systemic blood flows. The pulmonary arterial pressure continues to reflect the pressure in the ventricles.

The proper selection of patients for closure of ventricular septal defects cannot be judged by the mortality rate alone, since deaths may be associated with a complicating heart block, faulty technic in extracorporeal circulation, failure to close the defect completely and other technical surgical factors, as well as imperfect postoperative care. The success of the operation is determined in large part by the return of the circulation to normal or near to normal after closure of the defect. The persistence of severe pulmonary hypertension months after repair of a ventricular septal defect raises doubt as to the success of the operation.

The preoperative relationship of pulmonary arterial pressure to systemic pressure is in itself an unimportant criterion for the selection of patients for surgical intervention; the response of the pulmonary arterial pressure to repair is the important consideration. If the pulmonary flow does not exceed the systemic flow, an unsatisfactory response to closure of the defect is likely, and surgical treatment should not be offered.

Pulmonary and systemic blood flows may be calculated from the data obtained during cardiac catheterization. These data reflect the hemodynamic situation existing during the time of cardiac catheterization and may be influenced by artificial circumstances attending the procedure. Anesthesia or sedation, with resultant changes in pulmonary vascular resistance, pulmonary ventilation, and systemic oxygen saturation, may interfere with accurate interpretation of the data. Catheterization of a child without anesthesia may result in an unsteady physiologic state and may invalidate the formulas used for calculating systemic and pulmonary blood flows.

Evidence of increased left ventricular work in the electrocardiogram, with its concomitant increased pulmonary blood flow in a patient with ventricular septal defect should reflect the status of the shunts existing in the patient under those conditions present in his day-to-day living. Nadas[4] has not supported the views of Cabrera and Monroy[2] and has been unable to diagnose overloading of the left ventricle using their criteria. Fyler and associates[5] stressed the necessity of cardiac catheterization to define the size of the left-to-right shunt and the level of pulmonary vascular resistance in those patients who present electrocardiographic evidence of combined ventricular hypertrophy. Dreifuss and co-workers,[6] Zachariioudakis and associates,[7] and Char's group[8]

analyzed the electrocardiogram in cases of ventricular septal defect, measuring the voltage of the R, S, and T waves, and calculating values of R/S ratios; they found little or no correlation of the electrocardiogram with pulmonary blood flow, pulmonary pathologic changes, or surgical mortality rates.

The entire electrocardiogram must be studied carefully in searching for signs of left ventricular overwork. In some instances, lead V_6 may not be representative of the left ventricular potential, and one must examine leads II, III, and aV_F in some cases and leads I and aV_L or V_1 in others to assess the status of this chamber. The only evidence of left ventricular overloading in patients less than 3 years of age may be an axis deviation of the mean QRS vectors of +60 degrees or less or the presence of a counterclockwise QRS loop in the frontal plane, determined by vectorial analysis of the scalar electrocardiogram, features that are rarely seen in normal infants. Occasionally, Q waves greater than 0.4 mv. (4 mm.) are present in one or more of leads II, III, aV_F, and V_6 in infants less than 3 years of age without demonstrable cardiac disease, and this change may not, in the absence of other criteria, indicate overwork of the left ventricle.

The best proof of increased pulmonary blood flow is a decrease in pulmonary arterial pressure in relationship to systemic pressure immediately after the ventricular septal defect is closed. A comparison of electrocardiographic evidence of left ventricular overwork with the response of pulmonary arterial pressure after closure of the defect proved the validity of electrocardiographic interpretation of left ventricular overwork, inasmuch as 89 of the 90 patients with such evidence exhibited proof of increased pulmonary flow. The fact that 4 of the 10 patients not showing electrocardiographic evidence of left ventricular overwork had a slight to a moderate decrease in pulmonary pressure indicates that all information obtainable, whether clinical or physiologic, should be employed in selecting such patients for operation. We currently use this type of evaluation in clinical practice. Patterns of right ventricular hypertrophy were present in the electrocardiograms from all patients with ventricular septal defect in this study. Such patterns reflect pulmonary hypertension regardless of cause, whether primarily from increased pulmonary flow or from obliterative changes in the pulmonary vessels; thus, they are of no prognostic significance except as related to the associated presence or absence of evidence of left ventricular overwork.

Conclusions

The height of the pulmonary arterial pressure is in itself of no prognostic importance in determining which patients will have a successful response to surgical closure of a ventricular septal defect.

Of prime importance in the selection of patients for this operation is the relationship of the volume of blood flowing through the pulmonary and the systemic circuits. Those patients whose pulmonary blood flow is not in excess of the systemic flow, and who thus have a dominant right-to-left or a balanced shunt, will not experience a reduction in pulmonary arterial pressure after repair.

Electrocardiographic evidence of increased left ventricular work has proved to be of great value in assessing the pulmonary blood flow, regardless of the presence of severe pulmonary hypertension. Patterns of right ventricular hypertrophy in the electrocardiogram usually do not mask evidence of left ventricular overwork when the criteria suggested in this paper are applied, as evidenced by the 99 per cent correlation between electrocardiographic evidence of increased left ventricular work and proof of preexisting increased pulmonary flow in the 90 surgically treated patients with ventricular septal defect and severe pulmonary hypertension fulfilling such criteria.

On the basis of these observations, it is believed that the electrocardiogram has an important role in the selection of such patients for surgical treatment. In the absence of electrocardiographic evidence of left ventricular overwork, no patient should be denied surgical intervention if evidence for increased pulmonary flow can be obtained by any other means.

Summario in Interlingua

Le nivello del tension pulmono-arterial per se ha nulle importantia prognostic in determinar qual patientes respondera favorabilemente al clausion chirurgic de un defecto ventriculo-septal.

De prime importantia in le selection de patientes pro iste operation es le relation del volumine de sanguine que passa per le circuitos pulmonar e systemic. Patientes in qui le fluxo pulmonar non excede le fluxo systemic e in qui, per consequente, le shunting es dominantemente dextero-sinistre o balanciate non experientiara un reduction del tension pulmono-arterial post le reparo chirurgic.

Evidentia electrocardiographic de un augmento del travalio dextero-ventricular se ha provate de grande valor in le evalutation del fluxo de sanguine pulmonar sin reguardo al presentia de sever hypertension pulmonar. Configurationes electrocardiographic correspondente a hypertrophia dextero-ventricular non occulta le evidentia de excesso de travalio sinistro-ventricular si le criterios proponite in le presente articulo es applicate. Iste assertion pare esser justificate, viste le correlation de 99 pro cento inter le indicationes electrocardiographic de augmento del travalio sinistro-ventricular e le prova de un pre-existente augmento del fluxo pulmonar in le 90 chirurgicamente tractate patientes con defecto ventriculo-septal e hypertension pulmonar sever ubi le mentionate criterios esseva observate.

Super le base de iste observationes le opinion pare justificate que le electrocardiogramma ha un rolo importante in le selection, inter iste patientes, del casos appropriate al tractamento chirurgic. In le absentia de provas electrocardiographic de excessos de travalio sinistro-ventricular, nulle patiente deberea perder le beneficios del intervention chirurgic si le prova de un augmento del fluxo pulmonar pote esser obtenite per un altere methodo.

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So great was this Greek contribution to medicine that it is by no whim of chance that our medical terminology is so largely Greek in origin, that we call the essential method of medical reasoning the Hippocratic method, and that as heirs to so remarkable a heritage we choose to bind ourselves with the Hippocratic oath. For, following the Greeks, we now take disease to be an entirely reasonable process, obeying laws eventually patent to observation and to reasoning. There are exceptions, perhaps, to so categorical a eulogy of the Greek interpretation of the nature of disease. I doubt, for example, whether the Greeks maintained quite so detached, rational, and naturalistic a concept of mental diseases or epilepsy. But even if the Greeks had managed to be to some extent rational about insanity, the demoniac possession theories prevailed in later centuries. But in the main, the immense advantage of the Greek view was that, in the relative absence of superstition and fear, it built, with its amazingly rational approach, at least the scaffolding for the advancement of knowledge.—Alan Gregg, M.D. *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 32.

Auscultatory and Phonocardiographic Assessment of Pulmonary Stenosis with Intact Ventricular Septum

By Louis Vogelpoel, M.D., M.R.C.P. (Lond.), and Velva Schrire, M.B., M.Sc., Ph.D., M.R.C.P. (Lond. and Edin.)

THE COMPLETE diagnosis in a case of pulmonary stenosis must include correct assessment of the anatomic situation as well as its severity. In 2 previous studies[1, 2] concerning the differentiation of severe pulmonary stenosis with intact ventricular septum from Fallot's tetralogy a striking difference was found in the duration of the systolic murmur that enabled the anatomic diagnosis to be settled by bedside auscultation. It was also shown that the severity of the stenosis influences the duration of the murmur in opposite fashion in the 2 conditions. Increasingly severe stenosis lengthened the murmur when the ventricular septum was intact but shortened it when a large septal defect was present (Fallot's tetralogy). The different behavior of the murmur was dependent on the different dynamic situation in the 2 conditions.

The purpose of this paper is to draw attention to the value of auscultation and phonocardiography in diagnosing the severity of stenosis when the ventricular septum is intact. Their value in Fallot's tetralogy is described in a separate paper.[3] Reliable criteria based on the murmur length and width of splitting of the second sound will be defined, enabling accurate prediction of the severity of the stenosis. These are of considerable value in assessing the result of surgery.[4]

Severity of stenosis in cases with intact ventricular septum is most precisely determined by cardiac catheterization, but we believe that auscultation and phonocardiography are superior to other clinical methods such as electrocardiography and radiology. In the tetralogy, however, it is not sufficiently appreciated that electrocardiography, radiology, and even cardiac catheterization are usually not helpful in assessing severity, whereas auscultation and phonocardiography are accurate, simple, and invaluable for this purpose.[3]

Diagnosis of the severity of the stenosis is of great importance, since the symptomatology, natural history, and management are determined by the degree of stenosis in both conditions. While this statement is obviously true when the ventricular septum is intact, it also holds for the tetralogy because surgical relief of the stenosis alone results in disappearance of symptoms and cyanosis, despite persistence of the ventricular septal defect.[5, 6]

Material and Methods

Forty-three cases of pulmonary valvular stenosis and 8 of infundibular stenosis with intact ventricular septum were studied. The diagnoses were confirmed in all by cardiac catheterization and angiocardiography, and in 19 cases at operation, by methods previously described.[1, 2] One case came to necropsy. All cases of pulmonary stenosis associated with a left-to-right shunt in the atria or ventricles were excluded from this study. Mild pulmonary stenosis was included only if the right ventricular pressure was elevated above 30 mm. Hg; below this value idiopathic dilatation of the pulmonary artery was diagnosed. No case in frank cardiac failure was included.

Full clinical examination with special attention to auscultation was carried out independently by us, after which data were compared and finally checked with the phonocardiogram. Particular attention was paid to the intensity and duration of the systolic murmur *at the site of its maximal intensity*. The intensity was graded from 1 to 6 and the duration was analyzed by noting whether the crescendo was in early, mid, or late systole, whether the murmur ended before, at, or extended beyond the aortic component of the second sound, and whether this sound was clear, partially buried, or obscured by the murmur. Splitting of the second

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This paper is part of an M.D. thesis submitted by one of us (L.V.) to the University of Cape Town.

heart sound was noted and, if present, the degree of splitting on held expiration was graded from 1 to 4, and the intensity of each component was noted. The first sound was studied during respiration and held expiration for its intensity, width of splitting, and the presence or absence of pulmonary or ejection sounds.[1] Sounds and murmurs in diastole were also noted.

High-frequency (logarithmic) sound tracings, which give an accurate graphic representation of human hearing,[7-9] were recorded in every case and frequently repeated from time to time, particularly in those cases subjected to surgery. A modified 2-channel Sanborn Stethocardiette was used in the early cases, but a 6-channel New Electronic Products (London) recording apparatus with 2 phonocardiograph channels was later substituted. Sound tracings were recorded synchronously with electrocardiographic, indirect carotid, and jugular tracings. In most cases sound recordings were repeated during cardiac catheterization to obtain synchronous phonocardiograms, right ventricular, or pulmonary artery tracings with external carotid artery tracings. Recordings were made in the mitral area, fourth intercostal space just to the left of the sternum, the third left intercostal space pulmonary area, and aortic area. The amplification chosen was purely qualitative, designed to give the best recording for the particular purpose. Thus, to record a very soft sound, greater amplification was used; conversely to measure more accurately the site in systole of the crescendo of a very loud murmur, less amplification was used. The degree of amplification was always noted, so that subsequent recordings, in particular those taken after surgery, could be compared at the same attenuation. This method was roughly quantitative when used on the same patient, provided no marked changes occurred in chest wall thickness, but a method of sound calibration would have been desirable. However, as this study was chiefly concerned with changes in duration of murmur and width of splitting of the second heart sound, accurate measurements of intensity were not required. Mitral and tricuspid components of split first sounds, aortic and pulmonary ejection sounds, and aortic and pulmonary components of split second sounds were identified by the methods previously described[1, 10] and were always measured during held expiration unless otherwise stated. Tracings recorded at high speed (80 mm. per second) were always measured from the onset of the deflections whether recorded in the phonocardiogram, electrocardiogram, or indirect or direct pulse recordings.

The systolic murmur was analyzed in suitable tracings recorded during expiration at the site of maximal intensity of the murmur. The crescendo and duration of the murmur were measured from the first component of the first sound to the peak and the end of the murmur, respectively. The time taken for the systolic murmur to reach its crescendo was expressed as a percentage of the time between the first heart sound and the aortic second sound (left ventricular systole). Thus, if the crescendo occurred in midsystole, it would be expressed as 50 per cent, whereas if it occurred at the aortic second sound it would be 100 per cent. Similarly, the total duration of the murmur was expressed as a percentage of the time between the first heart sound and the aortic sound, and if it extended beyond the aortic sound some figure above 100 per cent would be obtained (figs. 1 and 2). The degree to which the aortic second sound was buried by the murmur was also expressed as a percentage. This was obtained by expressing the mean amplitude of the murmur where it transected the sound, as a percentage of the mean amplitude of the sound. The degree of burying thus varied from 0 to 100 per cent (table 1, and fig. 3). All measurements were made in at least 10 different systoles and the mean was taken.

Routine electrocardiograms included the standard and unipolar limb leads and the precordial leads V_1 to V_7. V_{3R} was often included. The degree of right ventricular hypertrophy was assessed without reference to the clinical condition and graded from 1 to 4 in severity. Routine radiologic investigation included fluoroscopy and skiagrams.

The severity of valvular or infundibular stenosis with intact ventricular septum was assessed by the right ventricular pressure measured during cardiac catheterization under barbiturate or morphine sedation. An arbitrary grading was used as follows: When the systolic pressure was under 60 mm. Hg, stenosis was considered mild (14 cases); between 60 and 120 mm. Hg, moderate (10 cases); between 120 and 180 mm. Hg, severe (15 cases); and over 180 mm. Hg, very severe (4 cases) (table 1). Eight cases of infundibular stenosis were similarly graded (table 1). There were 1 mild case, 4 moderate cases, 1 severe case, and 2 very severe cases. In the 2 severe cases, the pressures exceeded 200 mm. Hg, and in both a very small ventricular septal defect of no dynamic significance was found at surgery.

Results

Valvular Stenosis

In pulmonary stenosis with intact ventricular septum increasingly severe stenosis results in progressive increase in pressure and duration of right ventricular systole.[1, 2, 11*]

*This statement holds only for cases not in right ventricular failure. Once failure, with or without tricuspid incompetence, occurs and a fall in cardiac output supervenes, the correlation between the pressure and duration of right ventricular systole with severity of stenosis will clearly become changed.

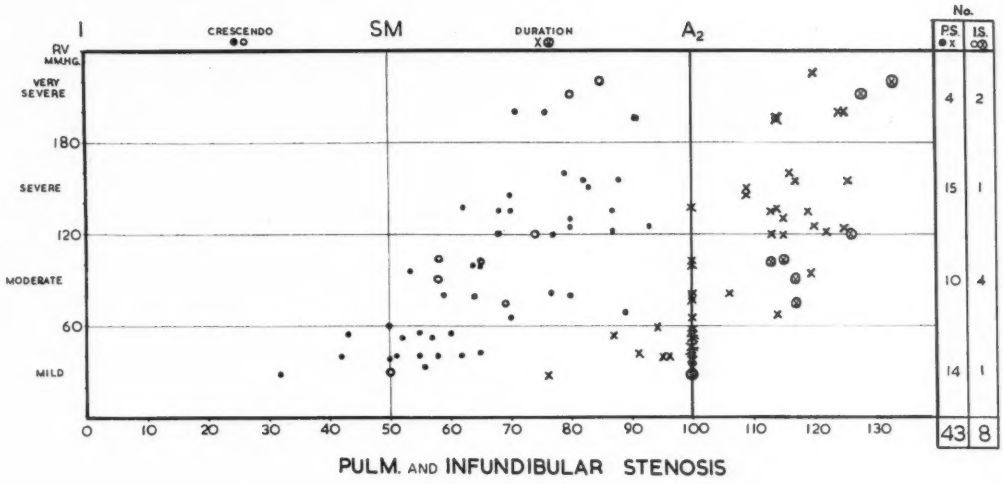

Figure 1

The relation of the crescendo (O) and duration (X) of the systolic murmur in 43 cases of pulmonary stenosis and 8 cases of infundibular stenosis (O and X respectively) to the duration of left ventricular systole (1-A_2). The severer the stenosis, as judged by the right ventricular systolic pressure, the greater was the duration of right ventricular systole as reflected by the crescendo and duration of the systolic murmur. The duration of the murmur appeared greater in infundibular stenosis than in valvular stenosis of comparable severity.

When stenosis is severe, both the pressure and the duration of right ventricular systole greatly exceed that of the left. The duration of the right ventricular systole in pulmonary stenosis can be detected clinically by the duration of the systolic murmur and the width of splitting of the second heart sound. It is now well recognized that with increasingly severe stenosis the murmur becomes more prolonged and the splitting wider.[1, 12-14] Conversely production of mild stenosis by a valvotomy promptly shortens the murmur and reduces the width of splitting.[4] (fig. 4).

In health, the 2 components of the second heart sound are fused or closely split on expiration (up to 0.03 second),[12] but are separate during inspiration, due to delay in the pulmonary component. In pulmonary stenosis splitting is abnormally wide due to greatly delayed closure of the pulmonary valve from prolongation of right ventricular systole.[1, 7] Since the aortic component marks the end of left ventricular systole and the pulmonary component the end of right ventricular systole, measurement of the width of separation of the 2 components gives a useful indication of the degree of prolongation and indirectly the pressure of right ventricular systole.[12] The duration of right ventricular systole can also be determined by the duration of the murmur with new methods of measurement. Since the murmur becomes prolonged with increasing duration of systole, it extends up to, into, or beyond the aortic second sound depending on the severity of the stenosis. Prolongation of right ventricular systole can therefore be measured by relating the duration of the murmur to the duration of left ventricular systole (time interval between first and aortic second sound). The ratio so obtained can be used to assess the severity of stenosis. The degree to which the aortic second sound is buried by the murmur reflects the intensity of the murmur at the termination of left ventricular systole providing another but indirect method of assessing the length of murmur.

In this study the duration of right ventric-

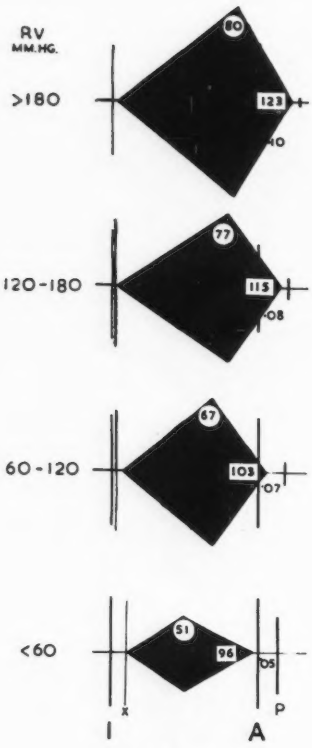

Figure 2

Illustrates the progressive prolongation of murmur length and width of splitting with increasing grades of severity of pulmonary stenosis with intact ventricular septum. The mean time of the crescendo and duration of the murmur, each expressed as a percentage of the duration of left ventricular systole, is indicated and drawn to scale for each group, as well as the mean width of splitting. With increasing severity the murmur becomes kite-shaped due to delay in the crescendo and marked lengthening of the murmur. The murmur progressively obscures more of the aortic component (A) but always ends before the pulmonary component (P), which becomes more delayed and softer. The pulmonary ejection sound (X) follows the first sound in the mild cases, but in severe grades coincides with the first sound as indicated.

ular systole determined by these methods has been correlated with the right ventricular systolic pressure in order to define criteria for assessing the severity of stenosis by auscultation and phonocardiography. The findings are analyzed in table 1 and figures 1, 2, 3, 5, and 6.

Mild Pulmonary Stenosis

There were 14 cases with a right ventricular systolic pressure under 60 mm. Hg. All had a soft to loud (grade 2 to 4) systolic murmur that reached a crescendo in midsystole and ended before or at the aortic component. The aortic component was always clearly audible. The second sound was abnormally widely split in expiration (mean 0.05 second), and the pulmonary component was not reduced in intensity. A pulmonary ejection sound was sometimes found (43 per cent of cases) but not invariably, as stated by Leatham and Weitzman.[12]

Moderate Pulmonary Stenosis

There were 10 cases with a right ventricular systolic pressure between 60 and 120 mm. Hg. The systolic murmur tended to be louder than in mild cases, the crescendo later than in midsystole and the duration greater, often extending beyond the aortic second sound. The aortic component was always audible, the degree of burying by the murmur being more than that found in mild pulmonary stenosis. The second sound was widely split in expiration (mean 0.07 second), and the pulmonary component was softer than normal. A pulmonary ejection sound was heard in 40 per cent of cases.

Severe Pulmonary Stenosis

There were 15 cases with a right ventricular systolic pressure between 120 and 180 mm. Hg. Five cases had cyanosis from a right-to-left interatrial shunt. The systolic murmur was loud (grade 3 to 5) in intensity, similar to the moderate and very severe groups. The crescendo occurred later than in the moderate cases and the duration was greater, extending well beyond the aortic component of the second sound. The murmur appeared kite-shaped rather than diamond-shaped. The aortic component was partially buried by the murmur in 6 cases and totally obscured in 8. Figure 3 shows that whenever the aortic sound was completely obscured by the murmur, the right ventricular pressure was above 120 mm. Hg. The murmur always ended before the pulmonary component, which was abnormally soft

Table 1

Analysis of Auscultatory and Phonocardiographic Findings in Pulmonary and Infundibular Stenosis with Intact Ventricular Septum

	Severity mm. Hg)	No. of cases	Systolic murmur: Intensity	Systolic murmur: Crescendo (% LV systole)	Systolic murmur: Duration (% LV systole)	Systolic murmur: % burying of A_2 by systolic murmur	A_2 in pulmonary area (auscultation)	P_2	Width of split (expiration) (sec.)	Aortic ejection sound	Pulmonary ejection sound
Valvular stenosis	Mild (RVP<60)	14	2-5	32- 65 (51)*	76-100 (96)	0- 42 (15)	N	N	0.02- 0.09 (0.05)	0	43%
	Moderate (RVP 60-120)	10	3-5	53- 89 (67)	94-117 (103)	0- 83 (37)	N	Soft	0.05- 0.12 (0.07)	0	40%
	Severe (RVP 120-180)	15	3-5	62- 93 (77)	100-125 (115)	36-100 (78)	Partially buried 6; buried 8	Soft (absent in 2)	0.06- 0.12 (0.08)	0	Click-like 1st sound 55%
	Very severe (RVP>180)	4	4-5	71- 88 (80)	120-125 (123)	100	Buried	Very soft (absent in 1)	0.09- 0.10 (0.10)	0	Click-like 1st sound 50%
	Total	43									
Infundibular stenosis	Mild (RVP<60)	1	5	50	100	20	N	N	0.07	0	0
	Moderate (RVP 60-120)	4	4-5	48- 69 (60)	115-117 (116)	56-100 (70)	N	Soft	0.09- 0.12 (0.10)	0	0
	Severe (120-180)	1	5	74	126	100	Almost buried	0	0.12	0	0
	Very severe (RVP>180)	2	5	80- 85	128-133	100	Buried	Very soft (absent in 1)	0.14	0	0
	Total	8									

*Figures in parentheses are mean values.

in 12 cases and inaudible in 2. Splitting on expiration tended to be wider than in moderate cases, averaging 0.08 second. Splitting could not be heard when the aortic component was buried but could be demonstrated and measured on the phonocardiogram (fig. 4).

The first sound in the third left interspace was abnormally loud on expiration in 8 cases. The loud sound coincided with the second component of a closely split first sound. Whether this was due to loud tricuspid valve closure or an unusually early pulmonary ejection sound could not be determined, but we favor the latter for the following reasons. The sound was sharp and click-like in quality. Its behavior with respiration was similar to the pulmonary ejection sound found in milder cases of pulmonary stenosis, being very loud at the onset of expiration yet often absent during inspiration (see fig. 9, Vogelpoel and Schrire[1]). In severe pulmonary stenosis in which the pulmonary diastolic pressure is low and, in consequence, the isometric contraction time of the right ventricle short, a pulmonary ejection sound would be early. It may indeed occur so early that confusion with tricuspid valve closure might result. Furthermore, in a severe case converted to a mild one by a successful valvotomy, the preoperative phonocardiogram revealed a loud "second component" of a closely split first sound, whereas the postoperative phonocardiogram showed a clear pulmonary ejection sound following normal splitting of the first heart sound (fig. 4). It was considered that an increase in isometric contraction time of the right ventricle would accompany conversion to mild stenosis and that this might shift a pulmonary ejection to a later position in systole, thereby clearly separating it from the first sound and making it recognizable as a pulmonary ejection sound.

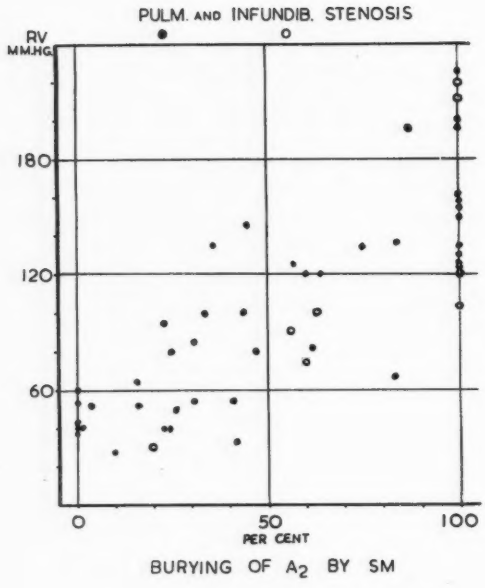

Figure 3

The degree of burying of the aortic component of the second sound by the systolic murmur in relation to the severity of the stenosis. This expresses the loudness of the murmur where it transects the aortic sound as a percentage of the amplitude of the sound. In both pulmonary and infundibular stenosis, the degree of burying steadily increases with increasing severity of the stenosis. In severe cases (RVP above 120 mm. Hg) the sound is usually partially or totally obscured. If the aortic sound is completely obscured the RVP is above 120 mm. Hg.

Very Severe Pulmonary Stenosis

There were 4 cases with a right ventricular pressure exceeding 180 mm. Hg. In 2, the pressure was above 200 mm. Hg. Two cases had cyanosis from a right-to-left interatrial shunt. The systolic murmur was very loud (grade 4 to 5), extremely prolonged and kite-shaped with the crescendo occurring very late and the duration invariably extending well beyond the aortic component. In every case the aortic component was completely buried by the murmur at the site of maximal intensity. The murmur always ended before the pulmonary second sound, which was abnormally soft and hence heard only in the pulmonary area. In 1 case it was inaudible and unrecordable.

Splitting could never be appreciated by the ear because the aortic component was completely obscured by murmur in the pulmonary area, which was the only site at which the very soft pulmonary component could be heard. At sites where the aortic component was audible, due to less intense murmur, the pulmonary component was inaudible. However, by using synchronously recorded phonocardiograms from the pulmonary area and the mitral area, the width of the splitting could be measured, provided the pulmonary component was recordable. In the 3 cases the width of splitting was very great, being 0.09, 0.10, and 0.10 second respectively. Since the width of splitting in cases with a buried aortic sound could not be heard, the only auscultatory guide to the excessive prolongation of right ventricular systole was the length of the murmur. The finding of a loud, very prolonged systolic murmur completely burying the aortic component but ending before a diminutive pulmonary component was sufficient to predict a right ventricular pressure exceeding 120 mm. Hg (fig. 3). The pulmonary component was always easy to distinguish from the aortic because it was so soft and always followed the end of the murmur.

A pulmonary ejection sound was not heard, but in 2 cases the first sound had a sharp click-like quality during expiration, similar to that found in severe stenosis. Other auscultatory findings of lesser value in assessing the severity of the stenosis were also found. An atrial sound and a presystolic murmur to the left of the sternum may occur in severe stenosis (see fig. 8, Vogelpoel and Schrire[1]). This has been ascribed to severe right atrial hypertrophy, where the giant "A" wave exceeded the pulmonary diastolic pressure. The pulmonary valve could thus be opened by this wave and pulmonary ejection initiated before the onset of right ventricular systole, resulting in the presystolic sound and murmur. A pulmonary incompetent murmur occurred in 3 cases, but was of no value in the assessment

of the severity of the stenosis occurring in moderate, severe, and very severe cases.

Comment

While auscultation alone permitted an accurate prediction of the grade of severity, study of the graphic recording made the assessment more certain. We found the length of the murmur of greater value than the width of splitting, since it was easier to assess on auscultation. In the analysis of the phonocardiogram, measurement of murmur length was also more dependable than the width of splitting (fig. 7, compare figs. 1 and 6).

Leatham and Weitzman[12] found a surprisingly close relation between the width of splitting and the right ventricular systolic pressure, bearing in mind that the phonocardiogram and cardiac catheterization were usually recorded on separate occasions. They emphasized the value of this method, since prolongation of right ventricular systole is measured in relation to left ventricular systole in the same patient and in the same cardiac cycle. However, the same advantage holds for measurements of the length of murmur. We confirmed their findings in the severe cases but found several important exceptions in the mild and moderate grades (fig. 6). In a mild case (RVP 42/4; PAP 16/1 mm. Hg) the width of splitting on expiration was 0.09 second (fig. 7). In a case of moderate severity (RVP 67/10; PAP 13/5 mm. Hg), the width of splitting was 0.12 second, and in a third case, also of moderate severity (RVP 65/0; PAP 17/2 mm. Hg), the split measured 0.10 second. In these cases, prediction of the right ventricular pressure from the width of splitting on expiration alone would have given an unreliable estimate of severity, but by use of criteria of murmur length, correct prediction was possible.

The reason for the exceptionally wide splitting found in these cases was obscure, as the usual causes could be excluded. Thus there was no right bundle-branch block to cause delay in onset of right ventricular systole, no shortening of left ventricular systole, and no case had a left-to-right shunt. A striking feature common to all 3 cases, however, was gross post-stenotic dilatation of the pulmonary artery, suggesting that this might be the determining factor (fig. 7). In support of this possibility is that dilatation of this magnitude was never encountered in the severer cases where the width of splitting more accurately reflected the severity. It is well known that the degree of post-stenotic dilatation bears no relation to the severity of stenosis.[2] It is in fact likely to be much greater and more variable in the milder cases where the lack of correlation with width of splitting is most apparent. We believe that the elastic recoil of the pulmonary artery may be an important, hitherto unrecognized, factor in influencing the time of closure of the pulmonary valve.

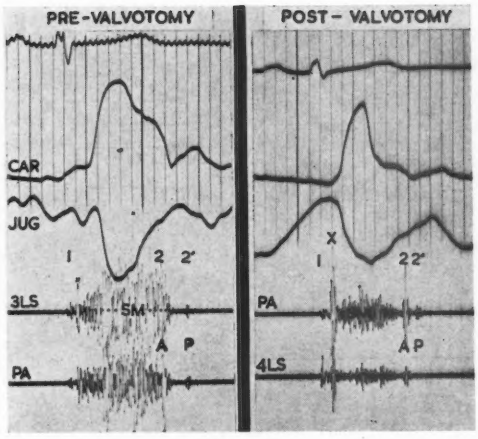

Figure 4

Pulmonary stenosis before and after valvotomy. Prior to surgery the murmur was very loud and prolonged, almost completely obscuring the aortic component at the site of maximal intensity (3LS). There was wide splitting (0.09 second) and a sharp click-like first sound on expiration. The features were those of severe stenosis; the RVP was 120/4 mm. Hg and PAP 18/10 mm. Hg. After valvotomy the murmur became softer and much shorter, the degree of splitting much less (0.04 second), and a striking pulmonary early systolic sound (X) emerged. The features were now those of mild stenosis, and an excellent result was predicted. This was confirmed on recatheterization 3 months after valvotomy (RVP 52/5, PAP 20/10 mm. Hg).

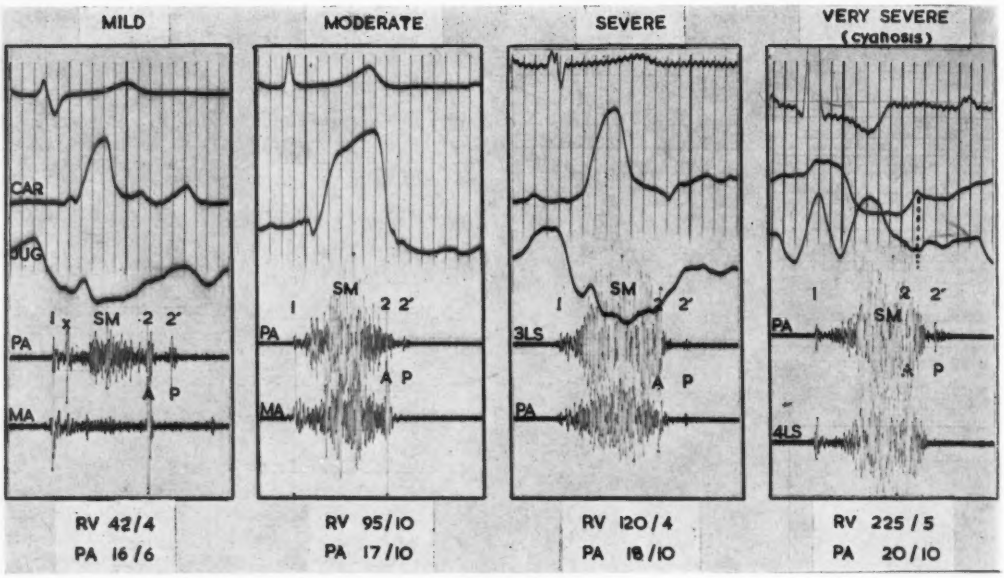

Figure 5

Pulmonary stenosis with intact ventricular septum. In the mild *case (RVP 42/4, PAP 16/6 mm. Hg) the crescendo of the systolic murmur was in midsystole and the murmur ended at the aortic component (A_2). The second sound was widely split (0.09 second), partly due to gross post-stenotic dilatation. There was a pulmonary ejection sound (X). In the* moderately severe *case (RVP 95/10, PAP 17/10 mm. Hg) the murmur was louder and extended a short distance beyond the aortic component, but did not obscure it. The pulmonary component was soft and delayed (0.07 second) after the aortic component. In the* severe case *(RVP 120/4, PAP 18/10 mm. Hg) the crescendo of the loud murmur was later and the murmur extended well beyond the aortic component, which it partially obscured. The pulmonary component was very soft and delayed 0.09 second. In the* very severe *case (RPV225/5, PAP 20/10 mm. Hg with right-to-left atrial shunt) the murmur was so prolonged that it extended far beyond the aortic component, which it completely obscured. The murmur ended before an easily audible pulmonary component that was followed by trivial pulmonary incompetence. The very wide splitting could not be heard but synchronous phonocardiograms at the pulmonary and mitral areas disclosed splitting of 0.11 second..*

In a greatly dilated pulmonary artery with thin inelastic walls, not only would there be greater delay in the filling of the vessels during ejection but the elastic recoil after ejection would be less vigorous. This might delay pulmonary valve closure quite independently of the duration and pressure of right ventricular systole. The low pulmonary diastolic pressure found in these cases may support such a mechanism, since none had pulmonary incompetence. It is of interest that we have found abnormally wide splitting in a few cases of idiopathic dilatation of the pulmonary artery in which no factors other than the dilated artery could account for the delay (up to 0.05 second in expiration in 1 case).

The disadvantage of assessing the severity from the width of splitting alone lies in the fact that in severer cases in which the correlation is good, splitting is usually inaudible; in the milder cases in which splitting is easily heard, the correlation is less reliable. If the murmur is relatively short, suggesting mild stenosis, but the splitting wide, suggesting severe stenosis, more reliance should be placed on the murmur. Such cases usually have mild

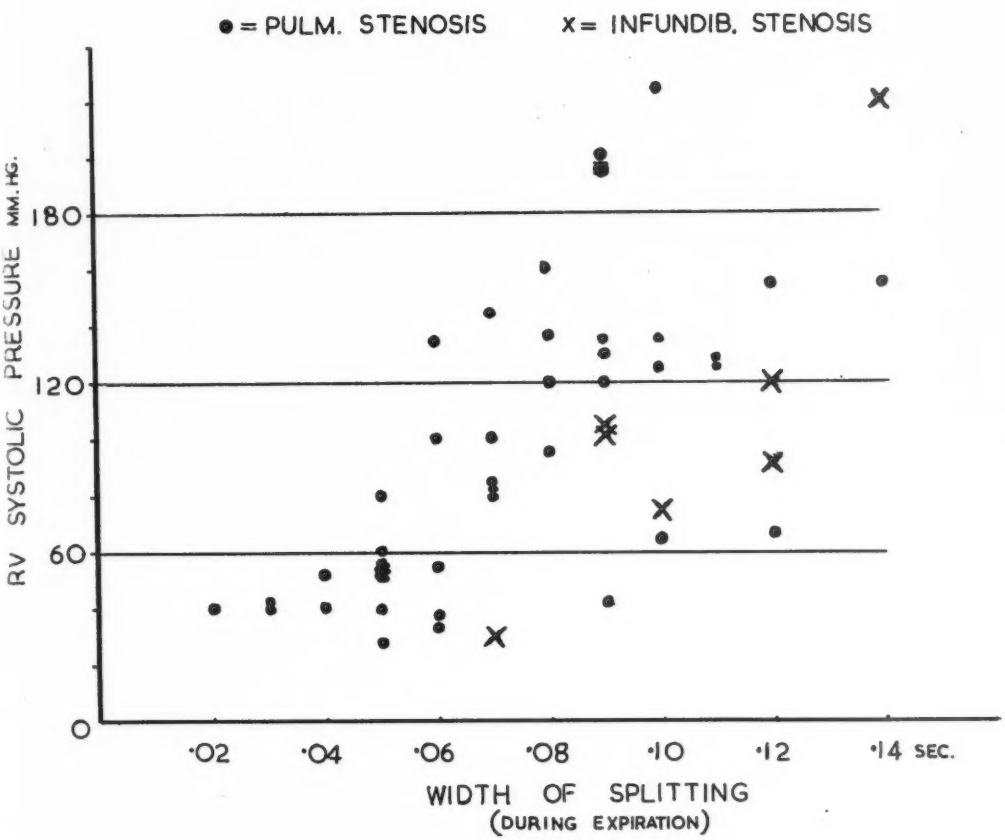

Figure 6

Relation of the width of splitting (delay in pulmonary valve closure) to the right ventricular systolic pressure in pulmonary valvular stenosis (●) and infundibular stenosis (X) to right ventricular systolic pressure. Unusually wide splitting was found in infundibular stenosis and in those cases of valvular stenosis associated with marked post-stenotic dilatation.

or moderate stenosis with marked post-stenotic dilatation.

There were 2 cases in which the length of the murmur was much shorter and the width of splitting narrower than expected for the height of right ventricular pressure. Both cases had left ventricular hypertrophy (moderate systemic hypertension, 200/125 mm. Hg in 1, and severe aortic stenosis (LVP 250/10, brachial arterial pressure, 85/60 mm. Hg) in the other. The reason for the shorter murmur, and hence the shorter duration of right ventricular systole, was not solely due to moderate prolongation of left ventricular systole. Possibly the hypertrophied left ventricle (and interventricular septum) enabled the right ventricle in some obscure fashion to achieve a high pressure (150 in the first case, 145 mm. Hg in the second) without the expected prolongation of systole.

The pulmonary ejection sound was of some value in grading the severity of the stenosis. If it occurred well after the first sound, producing "wide splitting" of the first sound in the pulmonary area, the stenosis was mild or moderate, but never severer than this (fig. 7).

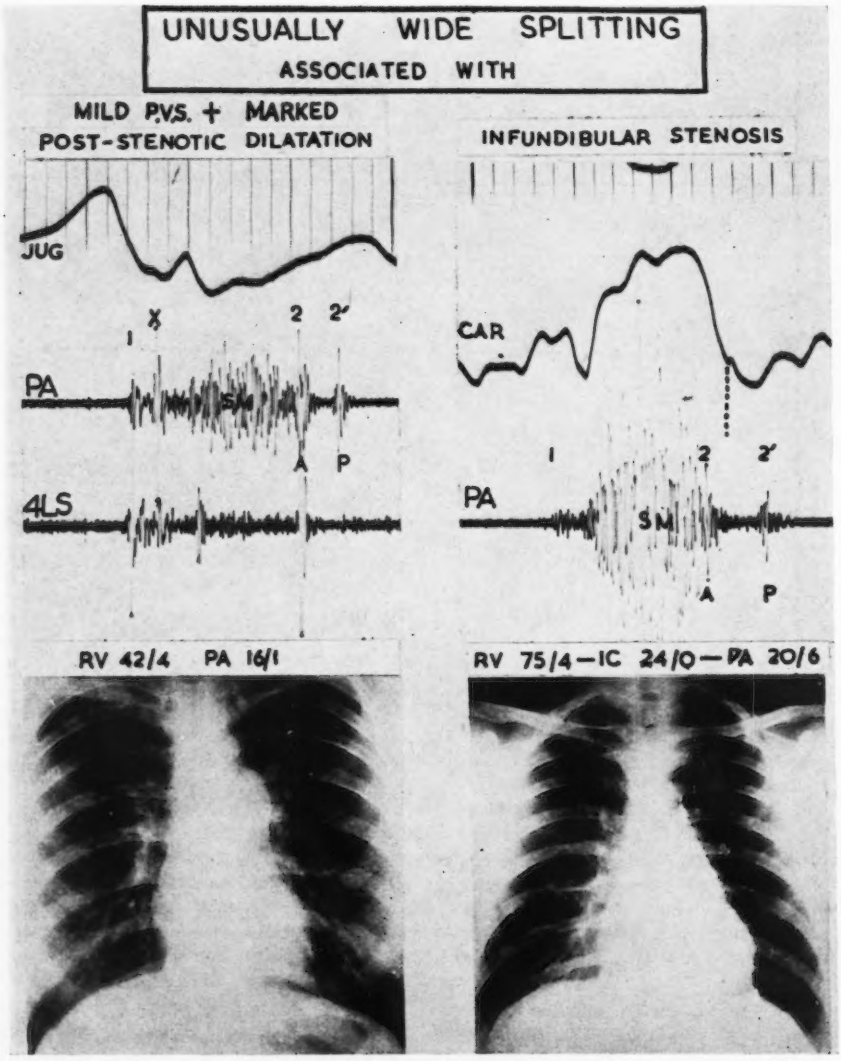

Figure 7

Unusually wide splitting in pulmonary and infundibular stenosis. In valvular stenosis the length of the murmur was that of mild stenosis, yet the delay in pulmonary valve closure was exceptionally great (0.09 second) and was attributed in part to the associated marked post-stenotic dilatation. The severity of the stenosis was correctly predicted by the length of the murmur but not by the width of splitting. In the case of the moderate infundibular stenosis the severity was correctly predicted by the length of the murmur but not by the gross splitting (0.12 second). The greater delay of pulmonary valve closure in infundibular stenosis cannot be attributed to post-stenotic dilatation but is probably due to delayed emptying of the infundibular chamber. Note the pulmonary ejection sound in mild valvular stenosis and its absence in infundibular stenosis.

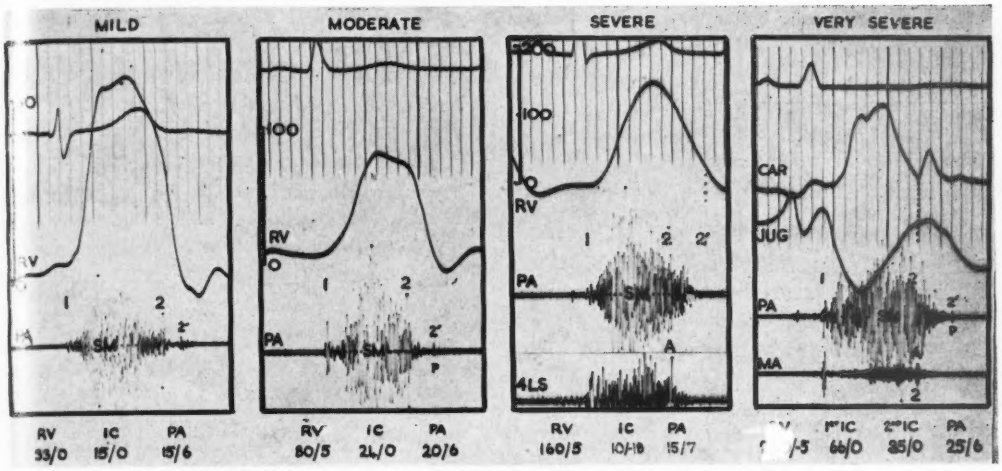

Figure 8

Infundibular stenosis with intact ventricular septum. The crescendo and duration of the systolic murmur became more delayed and the degree of splitting of the second sound wider with increasing severity of the stenosis, just as in valvular stenosis. In the severe and very severe cases the aortic component was completely obscured by the very prolonged murmur and the great width of splitting could not be heard; however, the synchronously recorded phonocardiogram from the mitral area (MA), where the murmur was much less loud, disclosed the site of the buried aortic component in the murmur, and the width of splitting could thus be measured (0.14 second). In infundibular stenosis the delay of pulmonary valve closure was greater than in valvular stenosis of equivalent severity, and there was no pulmonary ejection sound.

If, however, the first sound was either single or very closely split, being sharp and click-like on expiration, the stenosis was usually severe (fig. 4 and table 1).

Infundibular Stenosis with Intact Ventricular Septum

Whereas infundibular stenosis is much more commonly associated with a ventricular septal defect than with an intact ventricular septum, the latter situation is certainly encountered.

With increasingly severe infundibular stenosis the pressure and duration of right ventricular systole progressively increases to that found in valvular stenosis. Thus a similar correlation between the auscultatory findings and the right ventricular pressure would be anticipated. This was, in fact, found to be the case. In our small series of 8 cases a full spectrum of severity was fortunately encountered. Thus, there was 1 mild case, 4 moderate cases, 1 severe case, and 2 very severe cases (table 1 and figs. 1, 3, 6 and 8). In both of the latter there was an associated small ventricular septal defect of no physiologic significance. Similar small defects could not be detected in the other cases, but it is appreciated that the detection of minute septal defects can be extremely difficult. Additional confirmation of an intact or physiologically intact ventricular septum was obtained by the marked intensification of the murmur after amyl nitrite inhalation which excluded Fallot's tetralogy.[15,16]

Mild Infundibular Stenosis

In the 1 case the right ventricular pressure was 30/0, the infundibular pressure 15/0, and the pulmonary artery pressure 15/6 mm. Hg. The systolic murmur was very loud (grade 5), heard best in the third left interspace, with a crescendo in midsystole and

ending at the aortic second sound. The aortic second sound was clearly audible. Both components of the second sound were of normal intensity and splitting was unusually wide (0.07 second) compared to cases of valvular stenosis of comparable severity (figs. 6 and 8). There was no pulmonary ejection sound.

Moderate Infundibular Stenosis

There were 4 cases with right ventricular systolic pressures between 60 and 120 mm. Hg. None had additional valvular stenosis. One case had a right-to-left atrial shunt. The systolic murmur was very loud in all (grade 4 to 5) and more prolonged than in the mild case, with the crescendo at or after midsystole, and the duration exceeding that of the left ventricular systole. The aortic second sound was audible, being only partially obscured by the murmur. The pulmonary second sound was softer than normal and the width of splitting very wide (mean 0.10 second) (fig. 7). A pulmonary ejection sound was absent. The site of maximal intensity was in the third left interspace in all, so that distinction from valvular stenosis could not be made. The greater duration of the murmur (fig. 1) and the width of splitting compared to cases of valvular stenosis (fig. 6) are noteworthy.

Severe Infundibular Stenosis

There was only 1 case with a right ventricular pressure of 120/1 mm. Hg. The pressure in the infundibular chamber was 21/1, and in the pulmonary artery 16/10 mm. Hg. Central cyanosis was absent. The systolic murmur was very loud (grade 5), maximal in the third interspace with the crescendo after midsystole, ending well after the aortic second sound. The aortic component was completely obscured but the pulmonary component though inaudible was recorded, the width of splitting (0.12 second) being exceptionally great. There was no pulmonary ejection sound.

Very Severe Infundibular Stenosis

There were 2 cases both with right ventricular systolic pressures well above 180 mm. Hg. Both cases were of special interest, since small ventricular septal defects were discovered at ventriculotomy. Because of their small size and physiologic insignificance, the dynamics and physical signs were those of severe stenosis with intact ventricular septum.

The first case had a pressure of 220/−5 in the low right ventricle, far exceeding the systemic pressure of 135/100 mm. Hg. There were 2 pressure zones in the infundibular chamber, of 25/0 and 66/0 mm. Hg. The pulmonary arterial pressure was 24/6 mm. Hg. No shunt was detected, and the septum was considered intact. At ventriculotomy, by means of cardiopulmonary bypass, severe, low infundibular stenosis was found with a minute septal defect (2 mm. in diameter) opening into the infundibular chamber; the septum proximal to the stenosis was intact.

The systolic murmur was very loud (grade 5) and very prolonged (fig. 8), with a low site of maximal intensity (fourth left interspace). The crescendo occurred well beyond midsystole and the duration far exceeded left ventricular systole. The aortic sound was completely buried in the murmur. A very soft pulmonary second sound was audible. Splitting could not be heard, but the phonocardiogram showed great delay in pulmonary valve closure (0.14 second) (figs. 1, 6, and 8). There was no pulmonary ejection sound.

It may be argued that the small septal defect distal to the stenosis contributed a loud pansystolic murmur that would fuse with, and distort the shape of, the stenotic murmur. Indeed, the murmur of a small defect is frequently loud and has a late systolic crescendo.[16] However, such a murmur, being dependent on a left-to-right shunt, would end very soon after aortic valve closure and thus offer no contribution beyond this. Therefore the great prolongation of the murmur beyond the aortic second sound must be a function of the stenotic murmur, reflecting greatly prolonged right ventricular systole from very severe infundibular stenosis with intact proximal ventricular septum.

The second case had a right ventricular pressure far exceeding the left, and a small

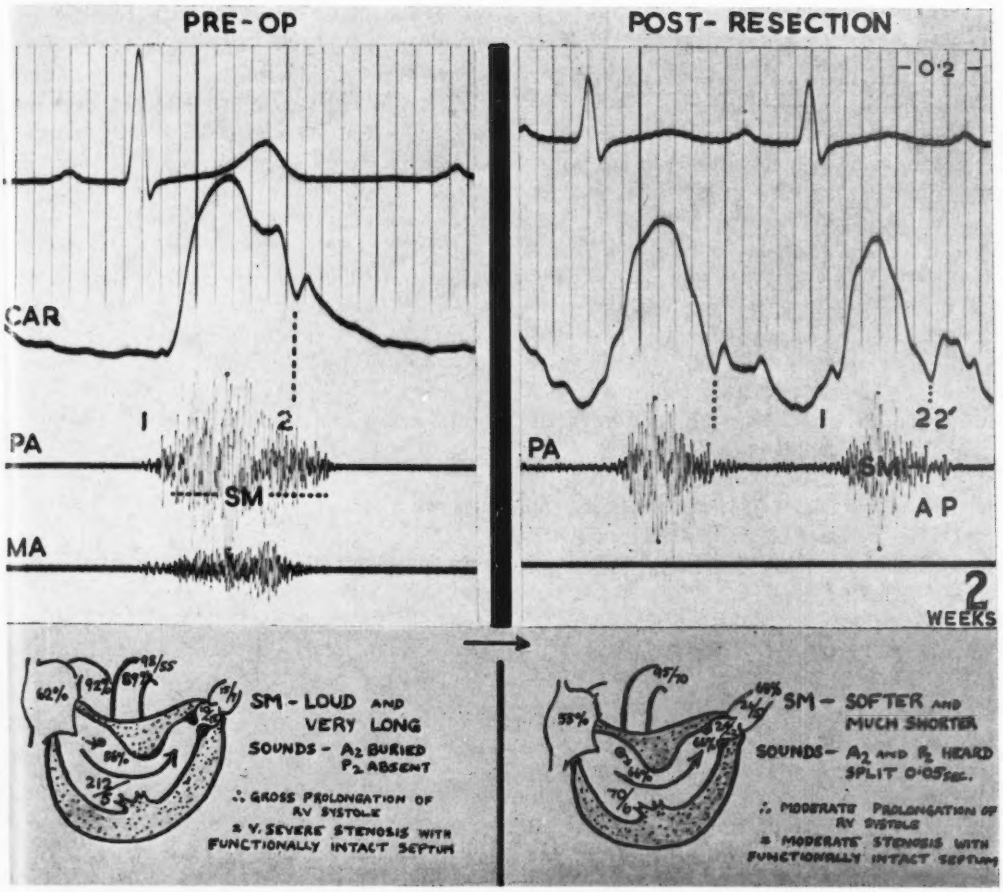

Figure 9

Infundibular stenosis with functionally intact ventricular septum. Owing to the small size of the septal defect the dynamics and murmur length before and after resection were those of intact ventricular septum. Note the postoperative shortening of the greatly prolonged systolic murmur, which far exceeded the duration of left ventricular systole. After resection the murmur length and width of splitting were those of moderately severe stenosis, and recatheterization 2 weeks after surgery confirmed this as well as a small left-to-right shunt.

right-to-left interatrial shunt through a patent foramen ovale was demonstrated at cardiac catheterization. The systolic murmur was very loud (grade 5), maximal in the pulmonary area, and very prolonged, with the crescendo well after midsystole, ending well after the aortic sound. The aortic sound was completely buried, and a pulmonary sound was neither audible nor recordable (fig. 9). There was no pulmonary ejection sound. The diagnosis of very severe pulmonary stenosis with intact ventricular septum was therefore made. At ventriculotomy under hypothermia a high infundibular stenosis was found, the pressure being 212/5 in the right ventricle, 10/—18 in the infundibulum, and 15/7 mm. Hg in the pulmonary artery. A catheter was passed from the right ventricle into the aorta where

the pressure was much lower than in the right ventricle.

Following the resection, the murmur shortened considerably and moderately wide splitting emerged, both suggesting that moderately severe stenosis had been produced. Catheterization performed 7 weeks after surgery showed a right ventricular pressure of 70/6 mm. Hg and a small left-to-right ventricular shunt (fig. 9). The defect was clearly of no physiologic significance, since the murmur shortened appropriately with the drop in right ventricular pressure from 212 to 70. Had the defect been large, as in Fallot's tetralogy, an infundibular resection would not have shortened the murmur.[4] The case masqueraded as severe infundibular stenosis with intact ventricular septum, since the septum was, in fact, functionally intact. A similar case with necropsy proof has been reported by McCord et al.[17]

Discussion

These findings confirm the belief that infundibular stenosis, whether high or low, influences the auscultatory findings in the same way as valvular stenosis, provided the ventricular septum is anatomically and functionally intact. By use of the length of the systolic murmur, the degree of burying of the aortic second sound, and the width of splitting, the severity of the stenosis can be predicted as in the case of valvular stenosis (figs. 1, 2, 3, and 6). Differentiation between infundibular and valvular stenosis can be most difficult, yet clearly the distinction is of great practical importance. The site of maximal intensity of the murmur proved of little value, since it was in the fourth left interspace in only 1 case. In the remainder, it was loudest in the third left interspace, a site frequently shared by valvular stenosis. However, a number of new auscultatory signs emerged that were of value in differentiating the 2 conditions.

A pulmonary ejection sound or a sharp click-like first sound was never encountered in infundibular stenosis in contrast to its frequent occurrence in valvular stenosis. This may be due to the much less marked poststenotic dilatation of the pulmonary artery in infundibular stenosis.

In infundibular stenosis the width of splitting appeared to be much greater than in valvular stenosis of comparable severity (fig. 6). Thus in the mild case the splitting measured 0.07 second, in the 2 moderate cases it was as much as 0.10 and 0.12 second (fig. 7) respectively, and in the severe case it was 0.1 second, and in the very severe case 0.14 second. The reason for the excessive delay in pulmonary valve closure in infundibular stenosis is obscure. Clearly it cannot be ascribed to abnormality in the pulmonary artery, since post-stenotic dilatation was not a feature of these cases (fig. 7). The mechanism is probably related to the duration of ejection of blood into the pulmonary artery. This may well be more prolonged in infundibular than in valvular stenosis due to delay in emptying of the abnormal, often dilated, infundibular chamber so frequently present. Delay in emptying of this chamber would be revealed by delayed closure of the valve and not by the murmur, since the chamber lies distal to the stenosis.

We were unable to confirm the suggestion[18] that in infundibular stenosis with intact septum the crescendo of the murmur occurs earlier than in cases of valvular stenosis. However, it did appear to be true in the tetralogy, in which infundibular stenosis caused an earlier crescendo and more rapid diminuendo than in those cases with valvular stenosis.[3] Figure 1 shows that in stenosis with intact ventricular septum there is good agreement between the time of the crescendo in valvular and infundibular stenosis of comparative severity. However, the duration of the murmur appears to be longer in infundibular stenosis. This may reflect an increase in the severity of the stenosis with contraction of the outflow tract of the right ventricle. The infundibular region is one of the last portions of the right ventricle to contract during systole,[18–22] and dynamic narrowing of the outflow tract may increase the stenosis during early of midsystole. This has been shown to occur by Rodbard

a id Shaffer,[20] who compared the pressure c irves recorded simultaneously in the right v ntricle and infundibular chamber. In 10 c it of 13 cases of infundibular stenosis the p ressure in the 2 chambers began to rise to- g ther during the isometric contraction and f r a variable time during the rapid ejection p hase, but thereafter the infundibular pres- s ire began to fall, even though the right ven- t icular pressure continued to rise. The pres- s ires did not become coincident again until t e end of ejection. We have confirmed this a d in a few cases have found that the dura- tion of systole in the infundibular chamber is considerably longer than in the proximal chamber.[3] In the tetralogy, sudden increase in stenosis with infundibular contraction has the very disadvantageous effect of diminishing the flow into the pulmonary artery and increasing the shunt down the aorta.[3] This is reflected by the earlier crescendo and rapid diminuendo of the murmur[3] and occasionally complete disappearance of murmur when severe spasm of the infundibular muscle causes a cyanotic or syncopal attack.[3, 19, 23] When the ventricular septum is intact, however, the right ventricle proximal to the stenosis has no escape route and is able to hypertrophy and adapt itself much more adequately to the stenosis, whether this remains fixed or increases during systole. That systole is greatly prolonged when the stenosis is severe is clearly shown by the greatly prolonged systolic murmur and the excessive width of splitting, though part of the latter may be caused by delayed contraction in the infundibular chamber.

It is possible that gross subvalvular muscle hypertrophy in cases of severe valvular stenosis[19, 24, 25] might cause additional functional or acquired infundibular stenosis. In our severe cases of valvular stenosis, however, we have been unable to detect any altered relation between severity of stenosis and length of systole or change in the site of murmur that would suggest additional infundibular stenosis. Acquired subvalvular stenosis is probably only detectable by auscultation when the murmur fails to shorten after a satisfactory valvotomy.[4] In such cases the pressure gradient shifts from valvular to infundibular level and dynamics become those of infundibular stenosis.[19]

Summary

A clinical and phonocardiographic study has been made on pulmonary and infundibular stenosis with intact ventricular septum, in order to determine the value of auscultation and phonocardiography in assessing the severity of the stenosis. There were 43 cases of pulmonary valve stenosis with intact ventricular septum and 8 cases of infundibular stenosis with intact ventricular septum.

The severity of the stenosis, as determined by the right ventricular pressure, was correlated with the duration of right ventricular systole, as determined both by the length of the systolic murmur and the width of splitting of the second heart sound. It was shown that increasingly severe stenosis resulted in progressive lengthening of the murmur in relation to the aortic second sound and delay in pulmonary valve closure. Criteria were defined whereby the severity of the stenosis could be predicted; these proved more accurate than other clinical methods.

In mild stenosis (RVP under 60 mm. Hg), the murmur was soft to loud in intensity, reached a crescendo in midsystole and ended before or at the aortic component of the second sound. The second sound was always abnormally split (average 0.05 second), and there was frequently a pulmonary ejection sound. In moderately severe stenosis (RVP 60 to 120 mm. Hg), the murmur was louder, the crescendo and duration greater, extending a short way beyond the aortic component, which it never obscured. Splitting was wider (average 0.07 second), and the pulmonary component was reduced in intensity. There was frequently a sharp, click-like first sound on expiration. In severe stenosis (RVP 120 to 180 mm. Hg), the murmur was loud with great delay in the crescendo and duration, resulting in a kite-shaped rather than a diamond-shaped configuration. It invariably ex-

tended well beyond the aortic component, which it either partially or completely buried. The murmur always ended before a very soft pulmonary component, which was widely separated from the aortic component (average 0.08 second). In very severe stenosis (RVP above 180 mm. Hg) the murmur was loud and so prolonged that it invariably obscured the aortic component, but ended before a very delayed (average 0.10 second) diminutive pulmonary component, which may or may not be heard. Whenever the aortic component was completely buried by the murmur, the great width of splitting could not be heard on auscultation, and phonocardiography was required for its detection. Thus, the length of murmur and the degree to which the aortic sound was buried were more useful auscultatory guides than the width of splitting in severe grades of stenosis. Whenever the aortic component was buried, a right ventricular pressure exceeding 120 mm. Hg could be predicted.

Unusually wide splitting of the second sound was encountered in a few mild and moderately severe cases of valvular stenosis. These cases all had pronounced post-stenotic dilatation of the pulmonary artery to which the delay in pulmonary valve closure was attributed. In these cases prediction of severity from murmur length was more reliable than from width of splitting.

Valvular and infundibular stenosis differed only in a few features. In infundibular stenosis, a pulmonary ejection sound was never encountered and the width of splitting was much greater than in valvular stenosis of comparable severity. The mechanism is discussed. The site of maximal intensity of the murmur was seldom helpful in differentiating valvular from infundibular stenosis. The increase in murmur length with increasing severity of stenosis was similar in both conditions.

Acknowledgment

We wish to thank members of the Staff of Groote Schuur Hospital for referring cases for investigation and the Superintendent, Dr. J. Burger, for his permission to publish our findings. We are particularly grateful to Dr. Maurice Nellen, Professor R. H. Goetz, and Dr. A. Swanepoel for their assistance and cooperation. We would like to acknowledge the great assistance received from our technicians, Mr. and Mrs. L. W. Piller and Miss S. Joseph, and Mr. Todt for his photographic services. We are also indebted to Mrs. C. M. Hall for typing and many other services.

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Summario in Interlingua

Esseva effectuate un studio clinic e phonocardiographic de stenosis pulmonar e infundibular in le presentia de un intacte septo ventricular. Le objectivo esseva determinar le valor del auscultation e del phonocardiographia in estimar le severitate del stenosis. Le material includite in le studio consiste de 43 casos de stenosis del valvula pulmonar con intacte septo ventricular e de 8 casos de stenosis infundibular equalmente con intacte septo ventricular.

Le severitate del stenosis, determinate per le mesuration del tension dextero-ventricular, esseva correlationate con le duration del systole dextero-ventricular, determinate tanto per mesurar le longor del murmure systolic como etiam per estimar le largor del fissura in le secunde sono cardiac. Esseva demonstrate que grados crescentemente sever de stenosis resultava in un prolongation progressive del murmure in relation al secunde sono aortic e le retardo del clausion del valvula pulmonar. Esseva elaborate criterios que permitte predicer le severitate del stenosis. Iste criterios se provava plus accurate que altere methodos clinic.

In casos de leve stenosis (con tensiones dextero-ventricular de minus que 60 mm de Hg), le murmure esseva de intensitate debile usque a forte, attingeva un crescendo al centro del systole, e se terminava ante o in le componente aortic del secunde sono. Le secunde sono monstrava semper un fissura anormal (con un valor medie de 0,05 secundas), e frequentemente un sono de ejection pulmonar esseva notate. In casos de stenosis moderatemente sever (con tensiones dextero-ventricular de inter 60 e 120 mm de Hg), le murmure esseva plus forte, le crescendo e le duration plus marcate, ultrapassante per un curte distantia le componente aortic le qual—nonobstante—esseva nunquam obscurate. Le fissura esseva plus large (con un valor medie de 0,07 secundas), e le componente pulmonar esseva reducite in su intensitate. Le prime sono representava frequentemente un specie de clic que esseva acute in expiration. In casos de sever

stenosis (con tensiones dextero-ventricular de inter 12[illegible] e 180 mm de Hg), le murmure esseva forte con un create retardo in crescendo e duration, resultante in un configuration deltoidic plus tosto que rhombic. Invariabilemente illo ultrapassava le componente aortic per un bon distantia, mascante lo partialmente o mesmo in toto. Le murmure se terminava semper ante un debilissime componente pulmonar, le qual esseva nettemente separate ab le componente aortic (per un intervallo medie de 0,08 secundas). In casos de severissime stenosis (con tensiones dextero-ventricular de plus que 180 mm de Hg), le murmure esseva forte e si prolongate que illo invariabilemente obscurava le componente aortic, sed illo se terminava ante un diminutive componente pulmonar que esseva grandemente retardate (per un intervallo medie de 0,10 secundas). A vices iste componente pulmonar non esseva audibile del toto. Quandocunque le componente aortic esseva mascate completemente per le murmure, le marcate largor del fissura non esseva detegibile per le medios del auscultation; pro deteger lo, methodos phonocardiographic debeva esser utilisate. Assi, le longor del murmure e le grado a que le sono aortic esseva mascate esseva plus utile como guidas auscultatori in casos de sever grados de stenosis que le largor del fissura. Quandocunque le componente aortic esseva mascate, un tension dextero-ventricular de plus que 120 mm de Hg poteva esser predicite.

Inusualmente large fissuras del secunde sono esseva incontrate in un micre numero de casos leve e moderatemente sever de stenosis valvular. Iste casos esseva omnes distinguite per un pronunciate dilatation post-stenotic del arteria pulmonar, e il esseva a isto que le retardo in le clausion del valvula pulmonar esseva attribuite. In tal casos le prediction del severitate super le base del longor del murmure esseva plus valide que super le base del largor del fissura.

Stenosis valvular e stenosis infundibular non differeva in multe aspectos. In casos de stenosis infundibular, nulle sono de ejection pulmonar esseva unquam incontrate, e le largor del fissura esseva multo plus grande que in casos de stenosis valvular de grados comparabile de severitate. Le mechanismo de iste facto es discutite. Le sito del intensitate maximal del murmure esseva rarmente de adjuta in le differentiation de stenosis valvular e stenosis infundibular. Le augmento del longor del murmure que occurreva con un augmento del severitate del stenosis esseva simile in le duo conditiones.

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Amplatz, K., Lester, R. G., Schiebbler, G. L., Adams, P., Jr., and Anderson, R. C.: The Roentgenologic Features of Ebstein's Anomaly of the Tricuspid Valve. Am. J. Roentgenol. 81: 788 (May), 1959.

In spite of the fact that the correct diagnosis of Ebstein's anomaly can be made on the basis of the plain roentgenogram, only 1 paper on this subject has appeared in the American radiologic literature. This anomaly is relatively rare, constituting probably less than 1 per cent of all congenital heart defects. The authors present data on 23 cases of this malformation seen at the University of Minnesota hospitals. The pathologic and clinical features are briefly reviewed. The roentgen features are correlated to the pathologic findings in the 8 cases autopsied. The most constant roentgenologic feature in advanced cases was the tremendously dilated right heart with normal or decreased pulmonary vasculature and absent left atrial enlargement. Pulmonary congestive changes and roentgen evidence of pleural effusion were strikingly absent even in the presence of right heart failure. Roentgen features are diagnostic in advanced cases but early stages of this disease may present essentially normal cardiac contours or mimic other congenital heart lesions.

KITCHELL

Auscultatory and Phonocardiographic Assessment of Fallot's Tetralogy

By Louis Vogelpoel, M.D., M.R.C.P. (Lond.), and Velva Schrire, M.B., M.Sc., Ph.D., M.R.C.P. (Lond. and Edin.)

IN PREVIOUS communications on the differentiation of Fallot's tetralogy from severe pulmonary stenosis with intact ventricular septum, attention was drawn to the striking difference in the duration of the systolic murmur.[1, 2] In the tetralogy, the murmur usually reaches a crescendo near midsystole and ends before or at the loud aortic second sound, which it does not obscure. In severe pulmonary stenosis with intact ventricular septum, the murmur is much more prolonged, reaching a crescendo late in systole and extending well beyond the aortic second sound, which it often completely obscures. The murmur ends before a very soft pulmonary second sound that is very widely separated from the aortic component. These features are easily recognized at the bedside, and the diagnosis is usually settled by auscultation.

It subsequently was shown[3] that the length of the systolic murmur accurately reflects the severity of the stenosis. However, the murmur behaves in opposite fashion in the two conditions with increasingly severe stenosis. Thus, in pulmonary stenosis with intact ventricular septum the more severe the stenosis, the longer and later is the murmur.[3, 4] In Fallot's tetralogy the more severe the stenosis, the shorter and earlier is the murmur.[1, 3] A successful valvotomy or infundibular resection produces an opposite change in the murmur, shortening it in pulmonary stenosis and lengthening in tetralogy.[3, 5] These striking differences were shown to be dependent on the different dynamic situation in the two conditions.

The purpose of this paper is to draw attention to the value and importance of auscultation and phonocardiography in assessing the severity of Fallot's tetralogy. In the tetralogy, unlike stenosis with intact ventricular septum, it is not sufficiently appreciated that electrocardiography, radiology, and even cardiac catheterization are usually not helpful in evaluating the severity. It will be shown, however, that the length of the murmur and other auscultatory signs are accurate, simple, and invaluable for this purpose. Since the symptomatology, natural history, and management are determined by the degree of stenosis, the importance of correct diagnosis of the severity needs no emphasis.

Material and Methods

Sixty-two cases of Fallot's tetralogy were studied. The diagnosis was confirmed in all by cardiac catheterization or angiocardiography, by methods previously described,[2] and by operation (27 cases), and by necropsy (19 cases). By Fallot's tetralogy is meant severe infundibular or valvular stenosis with large ventricular septal defect and right and left ventricular pressures of the same order. Even in acyanotic cases the stenosis is relatively severe, permitting bidirectional ventricular shunt or at most a small left-to-right shunt (up to 2 liters per minute at rest). We have excluded cases of large septal defect with large left-to-right shunt and mild pulmonary stenosis or small septal defects with mild pulmonary stenosis. Such situations in our view are not true examples of acyanotic Fallot's tetralogy, and have been discussed elsewhere.[6, 7] Clinical examinations were made and sound tracings, electrocardiograms, and roentgenograms were obtained as previously described.[4, 8–11]

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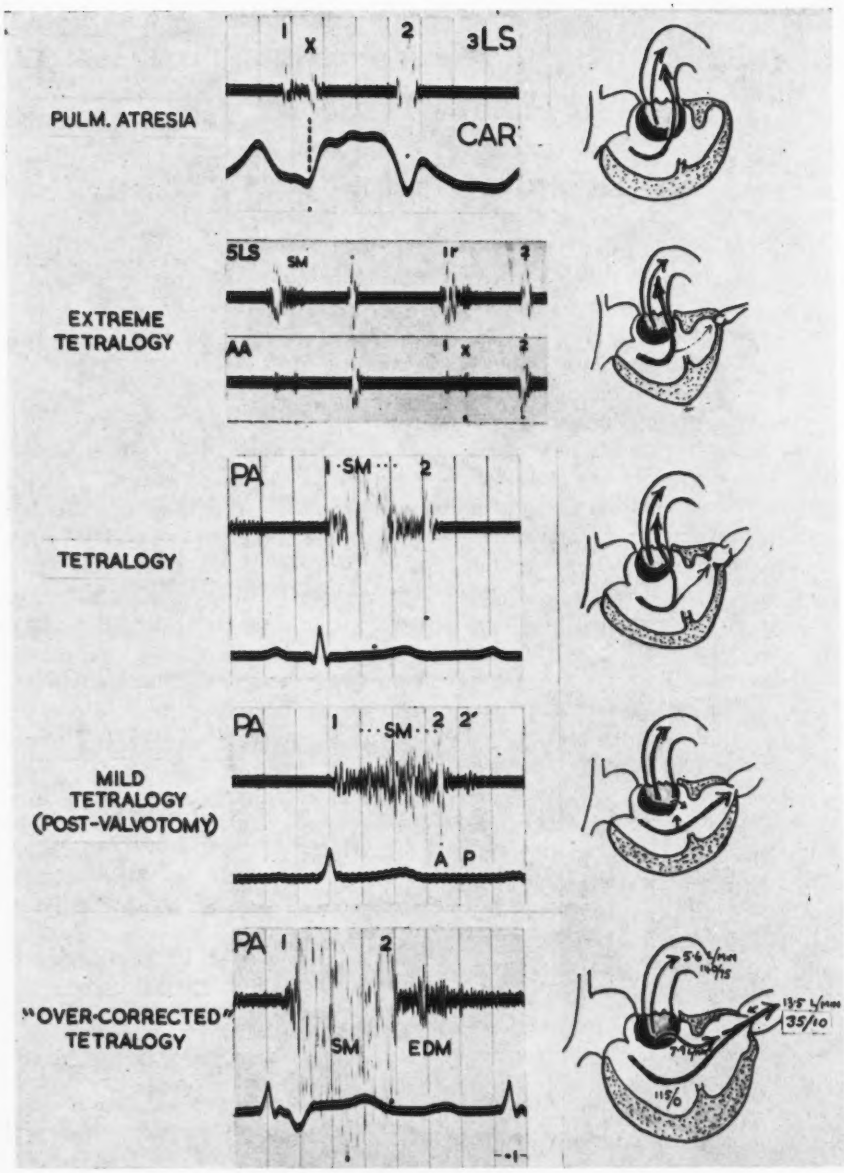

Figure 1

The relation between severity of stenosis and length and loudness of the murmur. In pulmonary atresia there is usually no systolic murmur but invariably a loud aortic ejection sound (X). In extreme tetralogy the murmur is soft, short, and confined to early systole, and there is usually an aortic ejection sound. In severe and moderate cases the murmur is loud but reaches a crescendo by midsystole and diminishes rapidly tc end before, or at, the loud aortic second sound. In mild cases the murmur is loud and more prolonged, extending into and occasionally slightly beyond the aortic component. A soft

(Continued at bottom of next page)

The severity of Fallot's tetralogy could not be as simply assessed as in pulmonary stenosis with intact ventricular septum.[4] The right ventricular systolic pressure remains at systemic level whether the stenosis is mild or severe, and thus fails to reveal the severity of the condition.[2] On the other hand, if the pulmonary blood flow and the degree of right-to-left shunt down the aorta could be accurately measured, a reasonable assessment of the severity of the condition would be possible. Our experience is similar to others,[12] however, in that with use of the Fick principle, calculations of blood flow in the tetralogy were not dependable for this purpose.

We have relied more on clinical methods of appraisal. The disability and degree of cyanosis were graded from 0 to 4, corresponding to nil, mild, moderate, severe, and extreme. Disability and cyanosis often correspond to the same grading and this correlated well with the degree of polycythemia. However, cyanosis was occasionally disproportionate to the disability, particularly in adults, of whom we had many cases. When cyanosis was severe yet symptoms mild and physical development normal, the degree of disability influenced the grading more than the cyanosis. On the other hand, in infants and physically retarded children it was difficult to apply the same method of grading used in ambulant children and adults. In our series there were very few infants but it is appreciated that grading is much more difficult in this age group, where hemodynamic adjustments are still taking place. However, it was not difficult to distinguish the extreme case with repeated cyanotic attacks from the mild case who was barely cyanosed and thriving, albeit a little slower than normal. It was generally simple, especially after several visits to the clinic and effort tests, to classify a given case. This was always done independently by us, and close agreement was the rule.

Extreme cases (6) were uncommon but readily recognized by their total disability and severe cyanosis (grade 4). Mild cases (21) although seldom completely symptom-free were able to live normal lives, did not often squat, were normally developed, were able to walk a reasonable distance on the level without stopping, and cyanosis was usually slight. Six of these cases were acyanotic at rest, and in several cyanosis would have been missed were it not for its appearance after effort or inhalation of amyl nitrite.[13] In 2 cases, cyanosis was grade 3, but the cases were classified as mild. The first, aged 30, was virtually symptom-free and doing an active day's work, as was the other, aged 19; both were normally developed. Moderate cases (17) were moderately disabled, usually with grade 2 or occasionally with grade 3 cyanosis and clubbing. Severe cases (18) usually had deep cyanosis (grade 3 to 4) and severely disabled, but not as totally incapacitated as the extreme case. In 3 cases, the cyanosis was only grade 1, but disability was severe. Two of these had syncopal attacks on slight effort and the third, an infant aged 2, the youngest in our series, had very frequent syncopal attacks at rest and was physically retarded.

Results and Comments

In the tetralogy, unlike pulmonary stenosis with intact ventricular septum the dynamic situation is completely altered by the presence of a large ventricular septal defect, which offers to the right ventricle an escape route of much lower resistance than its stenosed outflow tract, and hence the right ventricular systolic pressure cannot significantly exceed the systemic pressure.* Thus the right ventricular pressure is determined, not by the severity of the stenosis, but by the systemic resistance. Pulmonary blood flow is therefore dependent on 2 main factors, namely, the systemic resistance and the severity of the stenosis. For a given degree of stenosis, pulmonary blood flow will be influenced by the systemic resistance. If systemic resistance is high, the right ventricular pressure rises and increased pulmonary flow results;[14, 15] if the

*This argument holds for the majority of cases of tetralogy where the ventricular septal defect is large. It is appreciated that in the rare case of an exceptionally small septal defect[5, 16] or a large defect rendered functionally small by a tricuspid or endocardial flap valve,[17, 18] right ventricular pressure may adjust more satisfactorily to the stenosis by producing a higher pressure and a better gradient.

pulmonary component (P) is frequently recorded or often heard well after the aortic component (average 0.09 second) and reflects a relatively high diastolic pressure. In "over-corrected" tetralogy caused by excessive removal of the stenosis by valvotomy complicated by bacterial endocarditis a large left-to-right shunt developed through the large ventricular septal defect. A loud pansystolic murmur and pulmonary incompetence developed. The diagrams reflect the influence of the severity of the stenosis on the pulmonary blood flow and the ventricular shunt.

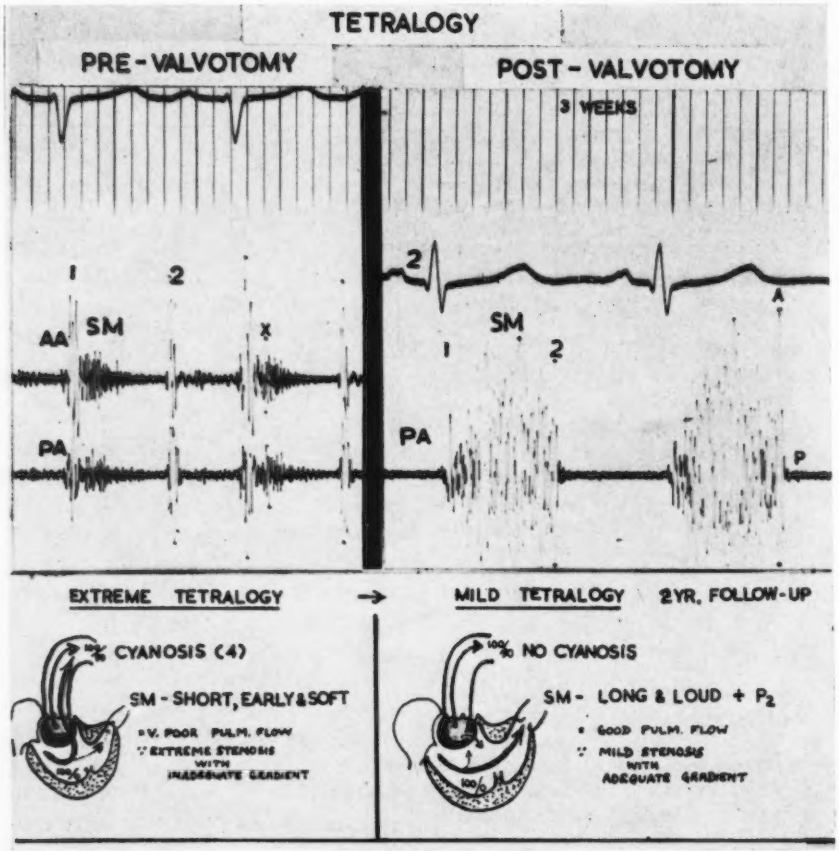

Figure 2

The effect of a successful valvotomy on the length and loudness of the systolic murmur. Extreme valvular stenosis rendered mild by valvotomy resulted in pronounced lengthening and intensification of the murmur and emergence of a very soft delayed pulmonary component. This proves that the murmur length and loudness are inversely related to the severity of the stenosis in the tetralogy and that the murmur is produced by the stenosis and not by the septal defect. The prevalvotomy and postvalvotomy sound tracings were recorded during expiration at the same attenuation. Each vertical line in this and subsequent tracings measures 0.04 second.

systemic resistance falls, following inhalation of amyl nitrite for example, the right ventricular pressure likewise falls causing decreased pulmonary flow with shortening and softening of the murmur.[13]

Conversely, for a constant systemic resistance, pulmonary blood flow diminishes with increasing severity of stenosis as shown by the inverse relation between the length and loudness of the murmur and the severity of stenosis (fig. 1).[1] Thus the severer the stenosis was, the shorter, softer, and more limited to early systole the murmur became. This is because the right ventricular pressure becomes progressively more inadequate the severer the stenosis; hence flow into the pulmonary artery becomes restricted to the early ejection phase of systole. During this phase the ventricle

Table 1

Analysis of Auscultatory and Phonocardiographic Findings in Fallot's Tetralogy

Severity	No. of cases	Systolic murmur: Intensity (1-6)	Systolic murmur: Crescendo (% LV systole)	Systolic murmur: Duration (% LV systole)	Systolic murmur: % burying of A_2 by systolic murmur	A_2 heard	P_2 on phono-card.	P_2 heard	Width of split (expiration) (sec.)	Aortic ejection sound	Pulmonary ejection sound
Extreme	6	1-2	26-30 (27)*	38- 55 (45)	0	6	0	0		6	0
Severe	18	2-5 (3)	22-60 (34)	68-100 (87)	0- 25 (4)	18	0	0		5	0
Moderate	17	3-5 (4)	30-87 (45)	80-101 (96)	0- 24 (10)	17	3	1	0.09	0	0
Mild	21	3-5 (4)	48-83 (69)	92-118 (102)	0-100 (32)	20	18	10	0.07-0.12 (0.09)	2	0
Total	62										

*Figures in parentheses are mean values.

contains most blood and attains its maximal pressure; thereafter pulmonary blood flow falls off sharply, since most of the stroke volume is discharged down the aorta. An important additional mechanism causing rapid fall-off in pulmonary blood flow and murmur in early systole may be the sudden increase in the stenosis produced by infundibular contraction later in systole.[17, 19, 21, 25] Clearly the influence of infundibular contraction on pulmonary flow will be more critical, the severer the stenosis is. By the time the aortic valve closes, both ventricles have discharged most of their blood down the aorta; hence the murmur usually ends before the aortic sound in severe cases. Conversely, it was shown that the milder the stenosis was, the longer the systolic murmur became.[1] This is because the right ventricular pressure produces a more satisfactory gradient the milder the stenosis. Thus the closer the pulmonary stenotic resistance approaches the systemic resistance, the longer is the duration of effective flow through the stenosed region and hence the longer the systolic murmur, which now extends into the aortic second sound (fig. 1).

These suppositions[1, 2] have been confirmed in 2 ways; firstly by correlating the auscultatory and phonocardiographic findings with the severity of the tetralogy and, secondly, by observing the marked increase in the duration of the systolic murmur that follows when a successful pulmonary valvotomy or infundibular resection results in a mild tetralogy[3, 5] (fig. 2).

The systolic murmur varied in intensity from grade 1 to grade 5. The intensity was of little value, however, in assessing the severity, except in extreme tetralogy where the murmur was never louder than grade 2 (table 1). Of far greater importance was the duration of the systolic murmur in relation to the aortic second sound at the site of maximal intensity of the murmur. This could be assessed with sufficient accuracy by auscultation, but sound tracings were always used to measure the length of murmur and degree to which the murmur buried the aortic second sound. The data thus obtained were correlated with severity of the tetralogy, as determined by the clinical method used. Figures 1, 3, 4, and 5 show that the severer the tetralogy, the shorter, earlier, and softer was the systolic murmur. The murmur thus behaves in opposite fashion to pulmonary stenosis with intact ventricular septum, where increasingly severe stenosis results in a longer, later, and louder murmur (fig. 5).

Extremely Severe Tetralogy

There were 6 cases, 2 with valvular stenosis, 3 with infundibular stenosis, and 1 with

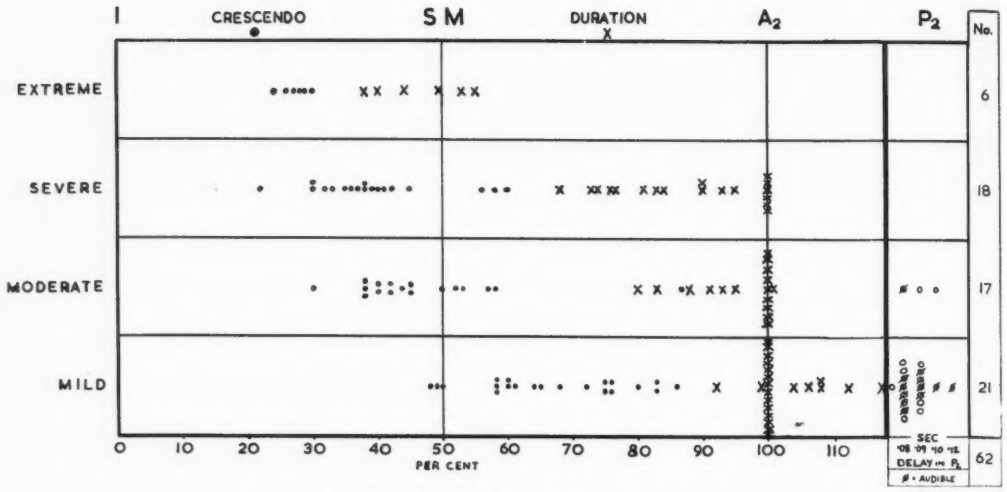

Figure 3

The time of the crescendo and duration of the systolic murmur in relation to left ventricular systole (1-A2) in 62 cases. The severer the stenosis as judged by the disability and cyanosis, the earlier is the crescendo and the shorter the murmur, proving the inverse relation between pulmonary flow, as reflected by the murmur and the severity of the stenosis. In mild cases, although the murmur usually ends in, and may be loud at, the aortic component, it rarely extends much beyond it. In 18 of 21 mild cases a delayed soft pulmonary component was recorded, and in 11 of these it was audible. A very soft pulmonary component was recorded in 3 moderately severe cases, being audible in 1.

both. Necropsy confirmed both the severity and site of stenosis in 4 cases, and in the fifth case extreme valvular stenosis was found at valvotomy, following which the case was converted into a mild tetralogy (fig. 2).

All had a soft systolic murmur (grade 1 to 2) confined to early systole, with the murmur ending long before the aortic second sound. The crescendo was early (table 1). The aortic second sound was loud, and in no case was the pulmonary component recorded. An aortic early systolic ejection sound was heard and recorded in all, and could be distinguished from pulmonary ejection sound by its wider range of audibility, lack of variation with respiration, and later onset in systole,[11, 22] giving the impression of "wide splitting" of the first sound at all areas. Confusion with the pulmonary ejection sound heard in pulmonary stenosis with intact ventricular septum never arose because the sound was only heard in mild and moderate patients all of whom were acyanotic.*

*We are in agreement with Leatham and Weitzman[23] that there is little need to distinguish between an aortic and pulmonary ejection sound in the cases with severe cyanosis and pulmonary stenosis. However, accurate distinction may be of paramount importance in differentiating severe tetralogy and pulmonary atresia from cyanotic heart disease associated with pulmonary hypertension. In both groups a short early systolic murmur and a loud unsplit second sound may be heard; but the first group has an aortic and the second a pulmonary ejection sound. The pulmonary ejection sound associated with pulmonary hypertension may closely simulate the aortic sound, since it occurs later in systole than it does in cases without pulmonary hypertension.[11] There is also much less variation with respiration, and it may occasionally be so loud that it becomes audible at all areas (personal observation). Hence great care must be exercised before assuming that an ejection sound in a cyanotic patient is of aortic or pulmonary origin, since on this decision the auscultatory diagnosis may be either correct or seriously misleading.

The aortic ejection sound in tetralogy is thought to be produced by several factors.[1] The aorta is dilated and nearer the chest wall than normally, because it is dextroposed and anteroposed and crossed by a pulmonary artery much smaller than normal. Furthermore, the severer the pulmonary stenosis, the greater is the stroke volume discharged into the aorta and the greater the likelihood of production of an ejection sound. However, its presence in milder cases may be obscured by the loud pulmonary systolic murmur commencing earlier in systole (ejection into the pulmonary artery precedes ejection into the aorta because the pulmonary diastolic pressure is much lower (fig. 7). We believe that a clearly audible aortic ejection sound usually indicates a severe tetralogy. In pulmonary atresia, in which the entire stroke volume of both ventricles is discharged into the very dilated aorta, a striking aortic ejection sound was the rule (fig. 1), as first described in an earlier publication.[1] Pulmonary atresia has not been included in this series, although it might well be regarded as the most extreme grade of tetralogy. However, when there is no communication between the pulmonary artery and the right ventricle, there can be no pulmonary stenosis, and hence the natural history and signs are dependent on factors not germane to the present discussion. The only relevant features are the almost invariable presence of a loud aortic ejection sound (11 of the 12 cases) and the frequent absence of a systolic murmur, supporting the belief that the ventricular septal defect plays no part in the genesis of the systolic murmur when the pressures in both ventricles are at the same level.

Severe Tetralogy

There were 18 cases in this category; 12 had infundibular stenosis, 2 were thought to have valvular stenosis, and 4 had infundibular and valvular stenosis. All had grade 3 disability and all but 3 had deep cyanosis and clubbing. The 3 exceptions had mild cyanosis, but had syncopal attacks in addition to marked disability. One had deep cyanosis and died in a cyanotic attack.

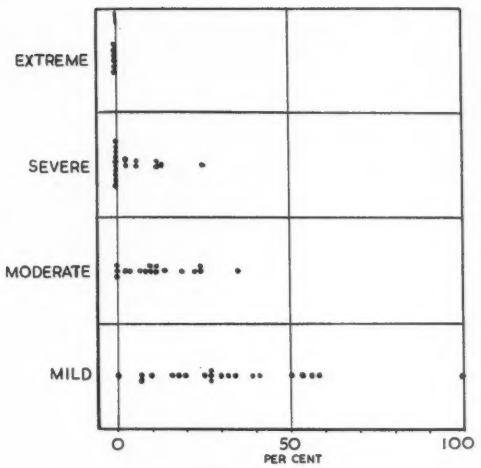

Figure 4

The degree of burying of the aortic second sound by murmur in 62 cases. This expresses the loudness of the murmur where it transects the aortic sound, as a percentage of the sound. The murmur was loudest at the aortic sound in the milder cases, but in only 5 did it exceed 50 per cent of the sound, and in only 1 case was the sound totally hidden by the murmur.

The systolic murmur, which was loud in all except 2 cases (grade 2 to 5), reached a crescendo before midsystole and ended well before the loud aortic second sound. Phonocardiographic analysis is given in table 1 and figures 3, 4, and 5. There was virtually no burying of the aortic second sound by the murmur (fig. 4). The pulmonary second sound was never recorded, and an aortic ejection sound was recorded in 5 cases although heard in only one.

Four cases had cyanotic or syncopal attacks. In 3 auscultation during an attack revealed disappearance of the murmur, despite the presence of marked tachycardia and a good pulse volume. These observations were consistent with the suggestion that such attacks may be due to temporary spasm of the infundibular portion of the right ventricle. One case died in a cyanotic attack, and severe infundibular stenosis was found at necropsy

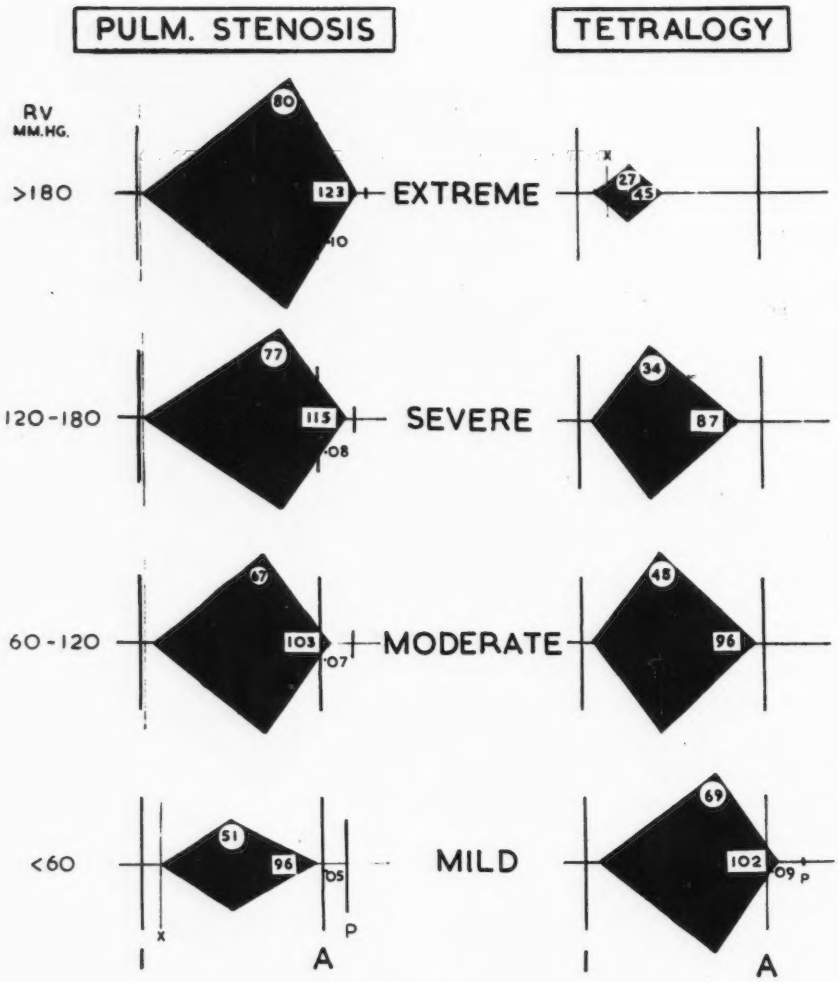

Figure 5

Illustrates the opposite effect induced on the murmur length by increasingly severe stenosis in pulmonary stenosis with intact ventricular septum and Fallot's tetralogy. The crescendo and duration of the murmur, each expressed as a percentage of the duration of left ventricular systole, have been drawn to scale by use of the mean times, as indicated, in each category of severity. The mean width of splitting of the second sound is also indicated. Increasingly severe pulmonary stenosis with intact septum causes a kite-shaped murmur due to great lengthening and delay in the crescendo. In severe stenosis the murmur usually totally obscures the aortic component (A) but always ends before the soft delayed pulmonary component (P). Increasing severity in the tetralogy causes the murmur to become shorter, softer, and more confined to early systole, and in extreme cases an aortic ejection sound usually emerges. A soft pulmonary component producing wide splitting is heard only in the mild cases. The murmur configuration of mild tetralogy is usually indistinguishable from moderately severe pulmonary stenosis.

fig. 10). Infundibular stenosis was also present in the other cases.

oderate Tetralogy

There were 17 cases; 10 had infundibular enosis, 1 was thought to have valvular stenosis, 4 had valvular and infundibular stenosis, and in the remaining cases the site could ot be determined. The systolic murmur, hich was loud in all (grade 3 to 5), reached crescendo at about midsystole and, to the ar, usually ended before or at the aortic econd sound, which was never obscured by he murmur. The second sound was loud, and wide splitting was audible in only 1 case. Phonocardiographic analysis is shown in table 1 and figures 3 and 5. The degree of burying of the aortic second sound by murmur was always very slight, and this could not be appreciated by ear. A pulmonary second sound was recorded in only 3 cases. It was extremely soft, occurring 0.09 second after the aortic component in all and just audible in one. In no case was an aortic ejection sound recorded.

Mild Tetralogy

There were 21 mild cases; infundibular stenosis was present in 10, infundibular and valvular stenosis in 2, and in 9 valvular stenosis was thought to be present. The high incidence of valvular stenosis in this group is noteworthy. All cases had mild disability; cyanosis was absent at rest in 6, but could be brought out by exercise and amyl nitrite.[13] Cyanotic attacks never occurred in this group.

The systolic murmur was loud in all (grade 3 to 5), reached a crescendo after midsystole, and extended into the aortic second sound. However, this sound was totally obscured by the murmur in only 1 case. A very soft second sound was audible in the pulmonary area in no less than 11 cases. It was always widely separated from the aortic component, causing wide splitting. In 3 cases it was quite loud and in 1 strikingly loud (fig. 6, Vogelpoel and Shrire[1]).

Phonocardiographic analysis (table 1) revealed that the crescendo occurred later in systole than in moderate tetralogy, and the duration was longer. The murmur was also louder at the second sound, though in only 1 case was it sufficiently loud to obscure the sound completely (fig. 4). This was in striking contrast to the severer grades of pulmonary stenosis with intact ventricular septum, where this sound was often totally obscured by the much more prolonged murmur[4] (fig. 5). The aortic component remained audible in the mild tetralogy, because this sound was usually louder than in pulmonary stenosis and, more important, the murmur was not so prolonged. The murmur continued for a short distance beyond the aortic sound in only 5 cases of mild tetralogy (fig. 3). Moreover, this was usually difficult to hear (fig. 6) and required an amplified phonocardiogram for confirmation.

An aortic ejection sound was recorded but not heard in 3 cases, being almost buried in the loud murmur that had commenced before it. A pulmonary ejection sound or sharp click-like first sound was never recorded or heard in contrast to its frequent occurrence in mild and moderate pulmonary stenosis with intact ventricular septum. This may be related to the greater post-stenotic dilatation and the larger stroke volume ejected into the pulmonary artery in the latter condition.

A very soft pulmonary second sound was recorded in 18 out of 21 cases, being audible in 11 (fig. 3). Splitting was always wide (mean 0.09 second). Phonocardiographic proof that the sound was the pulmonary component was based on its localization to the pulmonary area, its occurrence before the summit of the V wave in the synchronously recorded phlebogram[1] and its intensification after phenylephrine.[15] Of the 18 cases with a recordable pulmonary component, the stenosis was infundibular in 7, valvular and infundibular in 2, and valvular in 9. The sound was loudest when the stenosis was valvular. A recordable or audible pulmonary component always reflected an unusually high pulmonary arterial pressure for tetralogy. We first drew attention to the presence of splitting of the second sound and its significance in the tetralogy in an earlier publication,[1] and further experience has confirmed the view that a

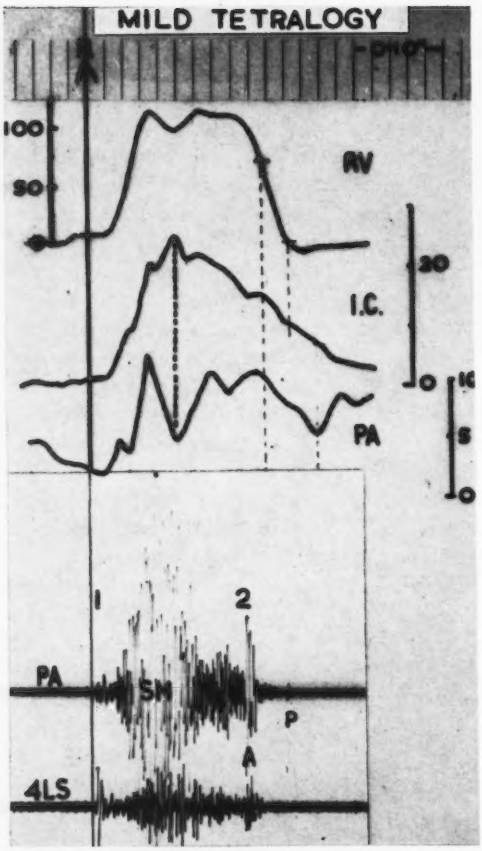

Figure 6

The influence of infundibular contraction on the crescendo and duration of the systolic murmur in a mild case of Fallot's tetralogy with infundibular stenosis. Allowing for a 0.02 second delay in transmission of pressure down the catheter, the peak of the crescendo coincided with peak rise of infundibular pressure (I.C.) and nadir of the Venturi wave in the pulmonary arterial tracing (PA), suggesting maximal pulmonary flow at this point. Thereafter, infundibular pressure fell while the proximal right ventricular pressure (RV) continued to rise. The rapid diminuendo of the murmur and disappearance of Venturi wave suggested abruptly reduced volume rate of pulmonary blood flow, probably due to increase in stenosis during infundibular contraction. Pulmonary valve closure (P) was delayed 0.09 second after aortic valve closure (A), presumably from prolonged isometric relaxation time and prolongation of systole in the infundibular chamber about 0.06 second beyond the proximal right ventricle. The figure has been constructed by superimposing sound and pressure recordings of identical cycle lengths and accurately mounted in relation to the R wave (R) of the same electrocardiographic lead.

recordable or audible pulmonary component is a valuable indication that the stenosis is mild in the tetralogy, since it denotes a relatively high pulmonary arterial pressure. That the component is a sensitive indication of the pulmonary arterial pressure in the tetralogy can be shown by its variable audibility with respiration, its temporary disappearance when blood flow and pressure are reduced following amyl nitrite inhalation,[13] and by its intensification when pulmonary blood flow and pressure are increased after phenylephrine.[15]

We believe that the murmur in mild tetralogy can never be as prolonged as in severe pulmonary stenosis with intact ventricular septum, despite the fact that splitting of the second sound, when measurable, is always as wide (average 0.09 second) (fig. 5). When the septum is intact the right ventricle can discharge its contents only through the stenosed outlet, hence the greatly prolonged systole and murmur when stenosis is severe. In the tetralogy, however, the large septal defect permits an alternative escape route, so that by the time of aortic valve closure the right ventricle has discharged most of its blood. Thereafter, despite persistence of a pressure gradient across the stenosis during the 0.09 second before pulmonary valve closure, little flow occurs. This is because the ventricle proximal to the stenosis is relaxing and contains little residual blood available for flow. Pulmonary valve closure is always delayed because time is required for the right ventricular pressure to drop from aortic to pulmonary diastolic pressure level. Since the pulmonary diastolic pressure is low and often at right atrial level the time interval between the aortic and pulmonary second sounds expresses the isometric relaxation time of the right ventricle in the tetralogy. The time is of the same order as that between the aortic sound and mitral opening snap in mitral stenosis.

nother important factor causing delay in pu monary closure in the tetralogy may be abnc mally prolonged contraction of the infundi ular chamber in cases with infundibular st osis. In the absence of additional valve st osis, delayed emptying of the infundibula chamber would be detected not by murmur bu by delay in pulmonary valve closure. Fi ure 6 shows that systole is in fact more pr longed in the infundibular chamber than in he proximal right ventricle. This case was an acyanotic tetralogy with infundibular stenosis. There was a 2.0 liter per minute left-to-right ventricular shunt. A large ventricular septal defect and relatively mild infundibular stenosis were found at ventriculotomy. Accurately superimposed sound and pressure tracings showed that the crescendo of the murmur occurred at midsystole, coinciding with the peak rise in infundibular pressure and the nadir of the Venturi wave in the pulmonary artery. Thereafter, the pressure in the infundibular chamber suddenly fell away, while the pressure in the proximal ventricle continued to rise. The decrescendo of the murmur coincided with the fall-off in infundibular pressure and descending limb of the Venturi wave in the pulmonary artery. This suggested that the stenosis was suddenly increased during systole of the infundibular chamber with abrupt reduction in volume rate of pulmonary flow. The murmur ceased shortly after the aortic second sound, but the pulmonary valve closed as late as 0.09 second after aortic valve closure, presumably due to prolonged systole in the chamber. Similar pressure and murmur changes have been found in other cases of infundibular stenosis, where tracings could be accurately superimposed. Figure 7 illustrates a severe case of tetralogy where the crescendo and sudden pressure drop in the infundibular chamber occurred earlier in systole. With the severe stenosis the influence of contraction of the chamber was presumably critical at an earlier period of systole than in the mild case discussed above. Despite the severer stenosis, the duration of systole in the infundibular

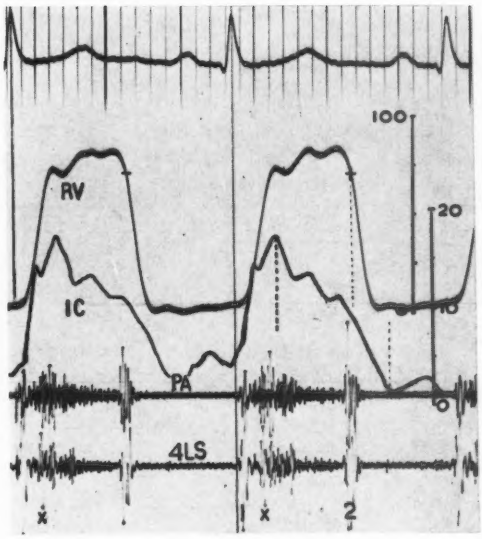

Figure 7

The influence of infundibular contraction on the murmur in a severe case with infundibular stenosis.

chamber also continued beyond that of the proximal ventricle. Had pulmonary closure been recordable, wide splitting would have been anticipated.

The incidence of valvular stenosis was much higher among the mild cases of tetralogy, whereas it was rare in the severer groups. This supports the belief that infundibular contraction greatly handicaps pulmonary flow when infundibular stenosis is present. Valvular stenosis would not be increased during contraction of the out-flow tract, and this may account for the tendency of the murmur to be longer with a later crescendo in mild cases with valvular stenosis. Even in mild cases with infundibular stenosis, the crescendo tended to occur earlier with a more pronounced diminuendo than in valvular stenosis (compare figs. 6 and 8, both of whom were acyanotic at rest).

Diastolic Murmurs

Diastolic murmurs were encountered in only 2 of the 62 cases. The first had aortic incompetence, since the early diastolic murmur followed the aortic second sound (fig. 8). She had infundibular stenosis of moderate severi-

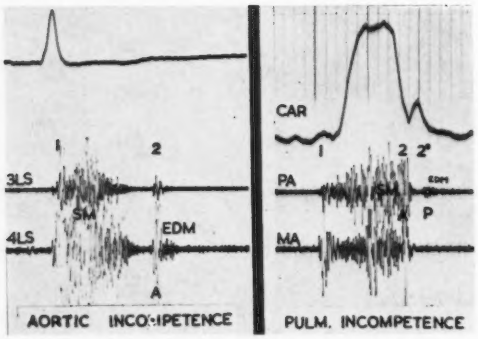

Figure 8

Diastolic murmurs in Fallot's tetralogy. The first case has moderately severe infundibular stenosis and aortic incompetence. The diastolic murmur in the second case was of pulmonary origin, since it commenced with the delayed soft pulmonary second sound (2,P), 0.08 second after the aortic second sound (2,A). The audible pulmonary sound and murmur proved helpful in predicting a normal pulmonary arterial pressure. This patient had relatively mild valvular stenosis and was acyanotic at rest.

ty as shown by the loud systolic murmur with early crescendo and rapid diminuendo. The diastolic murmur being aortic gave no guide as to the severity of the stenosis. The second case (fig. 8) had pulmonary incompetence, which proved a useful guide to the severity. The murmur could be distinguished from aortic incompetence by its delayed onset following the delayed and audible pulmonary second sound, occurring 0.08 second after the aortic sound. He had relatively mild valvular stenosis as shown by the loud systolic murmur with late crescendo and partial burying of the aortic sound. He was acyanotic at rest. The soft pulmonary second sound and incompetent murmur were of additional value, reflecting a relatively high pulmonary arterial pressure of 25/5 with a right and left ventricular pressure of 80/0 mm. Hg. Pulmonary incompetence not infrequently develops after surgery[5] and may follow an attack of bacterial endocarditis (fig. 6).

Mitral middiastolic flow murmurs were not audible in the acyanotic cases of tetralogy because none had a large left-to-right ventricular shunt. This murmur, however, is a useful indication of a large left-to-right ventricular shunt, being usually present in cases of large septal defect with mild pulmonary stenosis. Such cases, being excluded from this series by our definition of Fallot's tetralogy, will be discussed elsewhere.[6, 7]

Continuous murmurs from well developed bronchopulmonary collateral circulation were never heard in this series, in contrast to their frequent occurrence in pulmonary atresia. Diastolic sounds being rarely heard in the tetralogy[1] proved of no value in assessing the severity.

Discussion

We believe that the auscultatory criteria for assessing the severity of Fallot's tetralogy are of great value because they reflect the rate and volume of blood through the stenosed orifice. Hitherto objective methods have been limited to measurement of the left-to-right shunt down the aorta, since there has been no available simple method of assessing the pulmonary flow. Such criteria as the degree of central cyanosis, polycythemia, clubbing, and fall in arterial oxygen saturation during effort and the Valsalva maneuver, with use of ear oximetry, chiefly measure the right-to-left shunt (fig. 9). In practice, however, the length of the murmur alone will suffice, since in the tetralogy the less the pulmonary blood flow, the greater is the right-to-left shunt. Little experience is required to recognize and predict that a case with a loud, prolonged systolic murmur extending into, but not obscuring, the aortic component, whether or not associated with a soft pulmonary component, has good pulmonary blood flow. Cases showing these features are always virtually asymptomatic and often acyanotic at rest, and, in fact, frequently masquerade as cases of moderate pulmonary valvular or infundibular stenosis with intact ventricular septum (fig. 5) or small isolated ventricular septal defects requiring amyl nitrite for differentiation.[6, 13] They have relatively mild stenosis, sufficient to maintain balanced pressures in the ventricles with a slight left-to-right shunt, and a

vi tually normal pulmonary blood flow and p ssure. Conversely, severer cases with sl rter murmurs ending before a single second s nd are easily recognized, and the severity o the stenosis can be readily predicted from th e degree of shortening of the murmur.

It must be emphasized that the auscultatory a sessment of severity should be made in a r laxed subject examined at rest. This is be- a use pulmonary blood flow is dependent not o ly on the severity of stenosis but also on the ri ht ventricular pressure, which, in turn, is d termined by the systemic resistance. Marked changes in the latter may induce changes in the murmur independently of the stenosis. Elsewhere[13] we have shown that the brisk fall in systemic resistance following amyl nitrite inhalation induces a fall in right ventricular pressure despite the increased venous return to this chamber and the presence of pulmonary stenosis. This is due to the efficient escape route provided by the large ventricular septal defect. The fall in right ventricular pressure reduces pulmonary flow that is reflected by a marked temporary shortening and softening of the murmur. It is obvious that reduced systemic resistance from other causes will likewise shorten the murmur. Thus we have frequently observed marked shortening and softening in cases oversedated with morphine, pethedine, or barbiturates during cardiac catheterization. In such cases measurements of pulmonary blood flow and arterial oxygen saturation were often excessively low and might explain the inaccuracy of these methods in assessing the severity of Fallot's tetralogy by cardiac catheterization.[12] Conversely, increased systemic resistance results in elevation of right ventricular pressure that causes greater pulmonary blood flow,[14] a longer murmur, and less cyanosis.[15] We have reported on the favorable combination of coarctation of the aorta with Fallot's tetralogy[1] and the marked intensification of the murmur and increase in arterial oxygen saturation following pressor agents.[15] Squatting probably achieves its beneficial effect by combining increased systemic resistance with reduced venous return, and we have observed increase in loudness of the murmur during squatting. Partial clamping of the aorta during surgery is known to improve pulmonary blood flow, whereas excessive drop in systemic pressure has the opposite and highly undesirable effect.

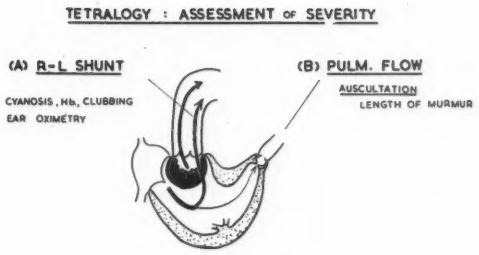

Figure 9

Illustrates the methods used at the bedside for objective assessment of severity in Fallot's tetralogy. Hitherto most methods have depended on measurement of the degree of right-to-left shunt down the aorta but auscultation conveys accurate information about the volume rate of pulmonary blood flow and hence the severity of the stenosis.

There are other variables that may influence pulmonary blood flow and murmur. Changes in cardiac rate, venous return, and blood viscosity must also play a greater or lesser part in the individual case. There is also the possibility that the state of tonus in the infundibulum may vary and so alter the degree of stenosis. However, the great merit of the murmur is that its length and loudness accurately reflect the volume rate of blood flow through the stenosis at the given moment. For this reason auscultation is a particularly sensitive means of detecting both the severity of the stenosis and the spontaneous fluctuations in pulmonary blood flow. Auscultation has in fact thrown considerable light on the mechanism of cyanotic and syncopal attacks to which severe cases of tetralogy are prone. In 4 cases examined during such attacks the murmur softened and shortened and at times completely disappeared (fig. 10). The presence of marked sinus tachycardia and a normal pulse pressure excluded acute hypotension as a cause of gross reduction in the gradient across the stenosis. In the presence of normal blood pressure and hence right ventricular pressure,

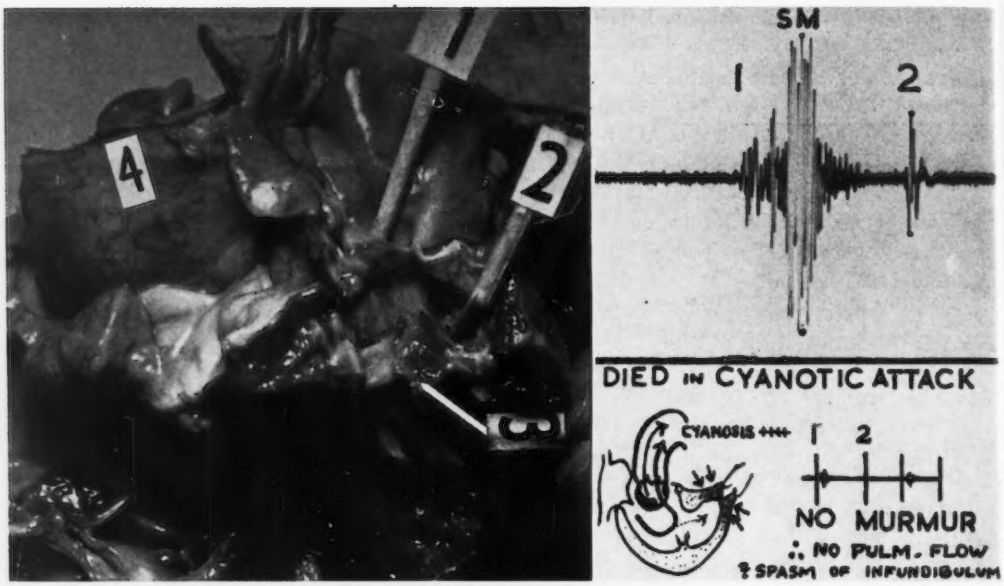

Figure 10

Severe Fallot's tetralogy. Two days before death the systolic murmur was loud but the crescendo occurred before midsystole followed by a rapid diminuendo with and cessation well before the loud aortic sound. These were the features of severe tetralogy. This child had had numerous cyanotic attacks for 2 years and had died in an attack. During an attack the murmur disappeared, despite a good pulse pressure. The concept of increased tonus of the infundibulum causing functional atresia, disappearance of the murmur, and a greatly increased right-to-left shunt is depicted in the diagram. The necropsy specimen shows the small infundibular chamber (2), between the pulmonary valves (1), and the severe infundibular stenosis. Small fleshy vegetations (3) are present in the chamber and thick contractile muscle surrounds the chamber. The tricuspid valve is shown in the lower left corner and the aorta (4) lies above.

disappearance of the murmur could only mean a greatly increased stenosis during the attack. On recovery from the attack, cyanosis lessened and consciousness returned while the murmur reappeared and returned to its original state, suggesting release of superadded functional obstruction. That increased tonus may occur in the infundibular portion of the right ventricle in Fallot's tetralogy has been well established[17, 19] and has been postulated as the mechanism of cyanotic attacks by Brock[17] and Wood.[24, 25] We believe that the shortening, softening, and eventual disappearance of the systolic murmur in the face of normal blood pressure confirm this suggestion. Brock[17] believes that cyanotic attacks are due to increase in tonus of an already diminutive outflow tract, which diminishes the lumen even further, as if by sphincteric action. Cyanosis is at once deepened by the marked increase in right-to-left shunt and the diminished blood flow to the lungs. The cases most prone to frequent, and perhaps fatal, cyanotic attacks are those in whom the stenosis is initially severe, where even a slight increase in tonus is sufficient to induce an attack. Wood[24] studied 5 cases of Fallot's tetralogy, either in an actual attack of syncope or in an episode of spontaneous dyspnea and cyanosis short of syncope. The blood pressure did not fall in any, and in 1 case Methedrine was without effect on the very low arterial oxygen saturation (10 per cent), even though the blood pressure rose from 100 to 150 mm. Hg

This proved that peripheral vasodilatation had not caused the attack; moreover, it strongly supported the contention of severe functional infundibular stenosis where even a right ventricular pressure of 150 mm. Hg failed to increase pulmonary blood flow. In all patients there was a shortening, softening, and eventual disappearance of the systolic murmur, according to the degree of fall in arterial oxygen saturation. When consciousness was lost, no murmur could be heard at all, suggesting that there was then a state of pulmonary "atresia." Unconsciousness was attributed to the extremely low arterial oxygen saturation. He concluded that the most likely mechanism accounting for these observations is that during the attacks the infundibulum contracts more completely than usual and tends to block the outflow to the lungs. This would cause the murmur to shorten and to disappear when the obstruction was complete.

If these views are correct then therapy should be aimed at release of the increased tonus in the infundibulum. Tonus must relax spontaneously in the majority of cases, possibly due to profound anoxia of the myocardium during the attack. Taussig observed that morphine has a most beneficial effect in relieving the attacks, but the mode of action is obscure. Could it be that it releases the tonus of the infundibulum? Wood[24] has shown that cyclopropane relieved the functional obstruction in 1 case of Fallot's tetralogy. Braudo and Zion[26] reported success with intravenous procaine in a mild, acyanotic case of Fallot's tetralogy that developed severe infundibular "spasm" during cardiac catheterization. This well-documented case proved beyond reasonable doubt that increased infundibular obstruction caused the cyanotic attack, since a normal blood pressure was maintained throughout while the murmur, which had been loud and long with an audible pulmonary component, disappeared. Procaine resulted in a temporary marked improvement in cyanosis, quick restoration of consciousness, and return of the murmur to its former loudness. However, morphine was ultimately required for complete recovery, since procaine released "spasm" only for a few minutes.

Table 2

Factors Influencing Pulmonary Blood Flow in Fallot's Tetralogy

(A)	Right ventricular-pulmonary arterial pressure gradient
(1)	*Increased by* (murmur gets longer and louder; right-to-left shunt diminishes):
	(a) *Lessening the severity of the stenosis*
	Surgery: infundibular resection or valvotomy
	Subacute bacterial endocarditis
	Relaxants of tonus of infundibulum, ? morphia, cyclopropane, oxygen, procaine
	(b) *Increasing systemic peripheral resistance*
	Hypertension
	Pressor agents
	Squatting
	(c) *Combining (a) and (b)*
(2)	*Decreased by* (murmur gets shorter and softer; right-to-left shunt increases):
	(a) *Increasing severity of the stenosis*
	Increased tonus of the infundibulum causing cyanotic attacks
	(b) *Decreasing systemic peripheral resistance*
	Inhalation of amyl nitrite
	Oversedation
	(c) *Combining (a) and (b)*
(B)	Bronchopulmonary collateral circulation (systolic murmur gives no information)
	Spontaneous development seldom effective, except in pulmonary atresia
	Increased by Blalock-Taussig and Pott's operations

The various factors that influence the blood flow through the stenosis and hence the systolic murmur in Fallot's tetralogy are summarized in table 2.

Summary

A clinical and phonocardiographic study has been made on 62 cases of Fallot's tetralogy in order to determine the value of auscultation and phonocardiography in assessing the severity of the stenosis.

The severity of the tetralogy, as determined by clinical methods, was correlated with the length and loudness of the murmur and other auscultatory signs.

Increasingly severe stenosis was shown to be associated with a shorter, earlier, and softer systolic murmur. In extreme tetralogy, the murmur was invariably soft and very short, being confined to early systole and end-

ing in midsystole. An aortic ejection sound was usually audible and the second sound invariably loud and single. In severe tetralogy, the murmur was usually loud and short, with its crescendo before midsystole and termination before the aortic second sound. A pulmonary component was never audible. In moderate cases, the murmur was loud and longer, with its crescendo at midsystole and termination before or at the aortic second sound, which was never obscured by the murmur. A very soft pulmonary component was only rarely recorded. In mild cases, the murmur was loud and more prolonged with the crescendo in the latter half of systole and extension into, but rarely much beyond, the aortic component. Although at times loud at the aortic component, the murmur totally obscured this sound in only 1 case. A pulmonary component was frequently recorded and often heard; it was extremely soft and localized, but occasionally relatively loud. Splitting was always wide (average 0.09 second). The loud, long murmur reflected good pulmonary flow; the audible or recordable pulmonary component, a relatively normal pulmonary arterial pressure.

Since the length and loudness of the systolic murmur reflect the volume rate of blood ejected through the stenosis, auscultation is believed to be a most valuable method of assessing both the severity of stenosis and fluctuations in blood flow, which may result from changes in systemic resistance and tonus of the infundibulum of the right ventricle. The change in murmur during cyanotic or syncopal attacks has thrown considerable light on the mechanism of such attacks.

Summario in Interlingua

Esseva effectuate un studio clinic e phonocardiographic de 62 casos de tetralogia de Fallot con le objectivo de determinar le valor del auscultation e del phonocardiographia in evalutar le severitate del stenosis.

Le severitate del tetralogia, determinate per methodos clinic, esseva correlationate con le longor e le fortia del murmure e de altere signos auscultatori.

Esseva monstrate que crescente grados de severitate del stenosis esseva associate con plus breve, plus precoce, e plus debile formas de murmure systolic. In tetralogia extreme, le murmure esseva invariabilemente debile e multo breve, con restriction al systole initial e terminate se durante le mesosystole. Un sono de ejection aortic esseva usualmente audibile, e le secunde sono esseva invariabilemente forte e unic. In sever tetralogia, le murmure esseva usualmente forte e breve, con su crescendo ante le mesosystole e su termination ante le secunde sono aortic. Un componente pulmonar non esseva unquam audibile. In casos de severitate moderate, le murmure esseva forte e plus longe, con su crescendo al mesosystole e su termination ante o ad le secunde sono aortic le qua esseva nunquam obscurate per le murmure. Un debilissime componente pulmonar esseva registrate in rar casos solmente. In leve casos, le murmure esseva forte e plus prolongate, con su crescendo in le secunde parte del systole, extendite usque a in le componente aortic sed rarmente usque a in ultra de illo. Ben que le murmure esseva a vices forte al momento del componente aortic, illo obscurava lo totalmente in non plus que un sol caso. Un componente pulmonar esseva frequentemente registrate; in multe casos illo esseva audibile. Illo esseva extremente debile e localisate, sed in certe casos su fortia esseva relativemente marcate. Le fissura esseva semper large (0,09 secundas). Le forte e prolongate murmure reflecteva un bon fluxo pulmonar. Le audibile (o registrabile) componente pulmonar reflecteva un relativemente normal tension pulmono-arterial.

Viste que le fortia e le longor del murmure systolic reflecte le volumine de sanguine ejicite per unitate de tempore via le stenosis, auscultation es considerate como un preciosissime methodo pro evalutar tanto le severitate del stenosis como etiam le fluctuationes del fluxo de sanguine le quales pote resultar de alterationes in le resistentia systemic e in le tono del infundibulo del ventriculo dextere. Le alteration in le murmure durante attaccos cyanotic o syncopic ha jectate multe lumine super le mechanismo de tal attaccos.

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Living is a state of becoming, not an unchanging finality. There are far deeper truths in the constancy of change than in the immutable permanence of death.—ALAN GREGG, M.D. *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 117.

Electrocardiogram in Asthmatic Children

By TERUMASA MIYAMOTO, M.D., IRVING KASS, M.D., AND MURRAY S. HOFFMAN, M.D.

THE electrocardiogram of presumably normal infants and children has been the subject of extensive investigation.[1-12] On the other hand, an extensive review of the literature failed to reveal reports of the electrocardiograms of infants and children suffering from pulmonary disease.[13, 14]

Ziegler[12] in 1951 recorded the electrocardiograms of normal infants and children ranging in age from birth to 16 years. Using only standard and unipolar extremity leads, he studied 250 children initially. Later complete electrocardiograms were taken on 300 children with the 3 standard extremity leads, augmented unipolar leads, and 6 unipolar precordial leads. Electrocardiograms of 137 children suffering from airway obstruction diagnosed as bronchial asthma are evaluated and compared with those of Ziegler's normal group.

Methods and Materials

A 13-lead electrocardiogram taken with a direct-writing instrument (General Electric Cardioscribe) was obtained on 137 asthmatic children in residence at the Jewish National Home for Asthmatic Children, Denver, Colorado. The patients had intractable bronchial asthma, which had not responded well to medical management prior to removal from home. Patients with acute severe obstruction were not studied until their airway obstruction lessened.

All electrocardiograms were recorded with the patient in the supine position. With the exception of the routine asthmatic regimen, no other medications were used. Ages of the patients ranged from 5 to 16 years. Table 1 shows the relationship between age and sex, and duration of symptoms.

The cardiac rate, duration of P wave, P-R interval, QRS complex, P-T interval, the amplitude of P waves, R waves, and S waves, and the time of onset of the intrinsicoid deflection were measured. The widest P wave, QRS complex, P-R interval, and Q-T interval were chosen for the measurement of the duration, as described by Ziegler. These figures were then compared with Ziegler's published data to see if there were any statistically valid variations from his normal electrocardiographic studies.

All data were subjected to the "t test" for unpaired data* in order to determine their statistical significance. Probability of less than 0.05, the usual level accepted for significance of biologic phenomena, indicated that the groups most likely did not come from the same population. For simplicity, only significant data have been presented.

Results

P Waves

The mean values of the amplitude of the P waves were lower in all the leads in all age groups of asthmatic children than in normal children.

Statistically significant results were found in all leads except lead III (table 2). There was also some prolongation of the P waves in the younger age groups (table 3).

R Waves

The R waves were lower in almost all leads in all age groups of asthmatic children than in normal children. This difference was especially pronounced in the precordial leads (table 4). Significant differences were found in leads I, aV_L, V_3, V_4, and V_5 in all age groups.

S Waves

There were no significant differences in the amplitude of S waves in the limb leads. In all age groups, however, the S wave in aV_R was

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* $$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{\Sigma (x_1 - \bar{x}_1)^2 + \Sigma (x_2 - \bar{x}_2)^2}{N_1 + N_2 - 2}\left(\frac{1}{N_1} + \frac{1}{N_1}\right)}}$$

$\bar{x}_1$ = mean of group 1
$\bar{x}_2$ = mean of group 2
$\Sigma(x-\bar{x})^2$ = sum of squares of the differences between the mean and each variate
N_1 = number of variates in group 1
N_2 = number of variates in group 2

Table 1

The Duration of Asthmatic Attacks Related to Age and Sex

Age groups (yrs.)	<2 yrs.	2-4*	4-6	6-8	Durations (years) 8-10	10-12	12-14	14-16	No. of cases
5- 8	0	6	10	9	0	0	0	0	25 {F 9 / M 16
8-12	1	1	7	19	19	18	0	0	65 {F 20 / M 45
12-16	1	2	7	7	4	15	6	5	47 {F 14 / M 33
								Total	137

*Between 2 years and the end of the third year.
F, female patients; M, male patients.

Table 2

*Mean Values of Amplitude of P Waves**

Age	Leads	I	II	III	aV_R	aV_L	aV_F	V_1	V_2	V_3	V_4	V_5	V_6
5- 8	N	1.1	1.7	0.8	–1.3	0.5	1.3	1.5	1.3	1.1	1.0	0.9	0.9
	A	0.5	1.0	0.5	–0.8	0	0.7	0.7	0.5	0.5	0.5	0.5	0.4
8-12	N	1.0	1.5	0.7	–1.3	0.6	1.2	1.4	1.3	1.1	1.0	0.9	0.8
	A	0.7	1.0	0.6	–0.8	0.1	0.8	0.5	0.6	0.5	0.4	0.5	0.5
12-16	N	1.0	1.6	0.9	–1.2	0.4	1.2	1.1	1.2	1.0	1.0	0.8	0.7
	A	0.6	1.0	0.5	–0.8	0.1	0.9	0.5	0.5	0.5	0.5	0.5	0.4

*Measured in 1/10 millivolt.
N, normal children; A, asthmatic children.

significantly smaller in the asthmatic children. In the right precordial leads, the asthmatic children showed a decreased amplitude of the S waves, which became significantly deeper in all age groups in the left precordial leads (table 5). When compared with normal children, the difference was statistically valid particularly in leads V_2, V_4, and V_5.

Intrinsicoid Deflection

The onset of the intrinsicoid deflection was delayed in the right precordial leads (V_1 and V_2) in all age groups of the asthmatic children; however, no significant difference was demonstrated in the left precordial leads, (V_5 and V_6) as shown in table 6.

Duration of QRS Interval

No difference was found in the 5 to 8-year-old group, but significant difference was demonstrated in the 8 to 12 and 12 to 16-year-old groups (table 7).

Heart Rate, Duration of P-R and Q-T Intervals

The heart rates, particularly in older age groups, were more rapid in asthmatic children (table 8). However, there was no statistical difference in the duration of P-R and Q-T intervals.

Table 3

Duration of P Waves

Age		No. of cases	$\bar{x}$*	S.E.†	t‡	P§
5- 8	N	90	.70	.010	5.0	<.001
	A	25	.80	.014		
8-12	N	88	.75	.011	5.13	<.001
	A	65	.83	.011		
12-16	N	68	.81	.012	1.71	.1>P>.05
	A	47	.84	.012		

*Mean value, measured in seconds.
†Standard error of the mean.
‡Value of t test.
§Probability.
N, normal children; A, asthmatic children.

Discussion

The electrocardiograms in the asthmatic children differed from the electrocardiograms of normal children as documented by Ziegler in the following important respects:

Table 4

*Mean Values of Amplitude of R Waves**

Age	Leads	I	II	III	aV_R	aV_L	aV_F	V_1	V_2	V_3	V_4	V_5	V_6
5- 8	N	6.1	12.2	8.3	1.6	2.5	9.1	6.7	11.5	13.1	25.3	20.2	13.4
	A	4.0	12.2	9.1	1.2	1.4	10.6	5.0	7.6	8.1	9.7	12.1	12.7
8-12	N	6.3	13.2	8.3	1.4	2.6	10.0	5.7	9.6	10.8	25.1	21.9	14.4
	A	4.2	11.8	8.6	1.4	1.3	10.0	4.5	7.1	8.0	12.8	12.1	11.4
12-16	N	5.6	13.2	8.6	1.3	2.4	1.3	4.8	8.1	10.4	22.2	17.2	12.8
	A	3.7	11.6	8.3	1.1	1.0	1.0	3.7	7.0	8.6	15.9	13.2	10.3

*Measured in 1/10 millivolt.
N, normal children; A, asthmatic children.

Table 5

*Mean Value of Amplitude of S Wave**

Age	Leads	I	II	III	aV_R	aV_L	aV_F	V_1	V_2	V_3	V_4	V_5	V_6
5- 8	N	2.1	1.5	0.9	4.8	2.9	1.0	12.7	22.2	15.0	6.6	2.4	1.0
	A	1.7	1.4	0.7	4.6	3.0	0.8	11.9	16.4	17.0	14.5	10.0	7.0
8-12	N	1.7	1.5	1.0	6.8	2.7	1.0	14.0	23.2	13.2	6.3	1.7	1.4
	A	1.6	2.0	1.2	5.1	3.1	0.8	10.5	15.5	14.6	11.6	7.9	4.7
12-16	N	1.4	1.4	0.9	6.1	2.4	0.9	13.4	22.0	10.6	4.6	1.8	1.1
	A	1.4	1.7	0.9	3.7	2.6	1.2	12.1	17.2	13.5	8.6	5.0	2.0

*Measured in 1/10 millivolt.
N, normal children; A, asthmatic children.

Table 6

Interval between Onset of QRS Complex and Onset of Intrinsicoid Deflection

Age		No. of cases	V_1 $\bar{x}$*	S.E.†	t‡	P§	V_6 $\bar{x}$	S.E.	t	P
5- 8	N	40 (41)**	.013	.0008	5.36	<.001	.029	.0010	1.36	>.1
	A	25	.021	.0014			.031	.0014		
8-12	N	44 (45)**	.014	.0009	6.8	<.001	.032	.0008	0.78	>.4
	A	65	.022	.0007			.033	.0008		
12-16	N	45	.013	.0010	7.3	<.001	.034	.0005	0.75	>.4
	A	47	.023	.0008			.033	.0011		

*Mean value, measured in seconds.
†Standard error of the mean.
‡Value of t test.
§Probability.
**No. in parentheses are number of cases, recorded in V_6.
N, normal children; A, asthmatic children.

P Waves

The P waves of the asthmatic children were lower in voltage than in normal children (table 2). The degree of pulmonary hyperinflation and the voltage of the P waves appeared to be related. In terms of specific resistance (ohm/cm.), Kaufman and Johnston[15] reported that the deflated lung had 401 ohm/cm.; inflated lung had 744 to 766 ohm/cm.; and superinflated lung had 1,227 to 1,367 ohm/cm. specific resistance. Table 9 reveals the results of chest x-rays in our asthmatic children: 18 per cent had increased roentgenographic radiolucency and 32 per cent had anterior bulging of the thorax. From these data it appeared that the low amplitude

of the P waves could be attributed not only to the pulmonary hyperinflation but to the secondary displacement of the heart.

R Waves

The R waves are generally low in voltage, especially in the left precordial leads, in asthmatic children (table 4). In 1930 Wilson[16] suggested the following factors as being theoretically responsible for lower voltage: lower potential produced by a diseased condition of heart muscle; accidental neutralization of effects of different parts of the heart; and changes in conductivity of tissues adjacent to the heart. The electrocardiograms of asthmatic children showed generalized low voltage of R waves as part of the effect of decreased pulmonary conductivity.

S Waves

If the excitatory process were still spreading through some part of the ventricular wall when the intrinsicoid deflection occurred, the negativity of the ventricular cavity should outlast this deflection and the S wave should be inscribed. In asthmatic children, S waves over the left precordium were remarkably deep in comparison with normal children (table 5). In right ventricular hypertrophy generally speaking, S waves are relatively prominent over the left precordial leads. Such changes may not be specifically diagnostic since they could be the result of simple rotation of a normal heart. It seems plausible, however, that the abnormally deep S waves in left precordial leads in asthmatic children may constitute an early sign of right ventricular hypertrophy.

Intrinsicoid Deflection

The intrinsicoid deflection is recorded when the activation wave reaches the subepicardial muscle of the heart underlying the exploring electrode.[17] The measurement of the time of onset of intrinsicoid deflection, particularly in the right precordial leads, is difficult and at times may be inaccurate. In this study there was slight delay in intrinsicoid deflections in right precordial leads in asthmatic as compared with normal children (table 6). This delay may be attributable to early right ventricular hypertrophy in asthmatic children.

Table 7

Duration of QRS Interval

Age		No. of cases	$\bar{x}$*	S.E.†	t‡	P§
5- 8	N	90	.07	.001	0	
	A	25	.07	.002		
8-12	N	87	.07	.001	6.2	<.001
	A	65	.08	.0012		
12-16	N	68	.07	.0012	5.8	<.001
	A	47	.08	.0014		

*Mean value, measured in seconds.
†Standard error of the mean.
‡Value of t test.
§Probability.
N, normal children; A, asthmatic children.

Table 8

Heart Rate

Age		No. of cases	$\bar{x}$*	S.E.†	t‡	P§
5- 8	N	90	96.2	1.8	1.07	.3<P<.2
	A	25	98.8	3.3		
8-12	N	88	78.5	1.6	4.2	<.001
	A	65	88.6	1.8		
12-16	N	66	75.4	1.6	4.3	<.001
	A	47	83.3	1.6		

*Mean value, measured per minutes.
†Standard error of the mean.
‡Value of t test.
§Probability.
N, normal children; A, asthmatic children.

Table 9

Chest X-ray Findings in 137 Asthmatic Children

Age group (yrs.)	Increased radiolucency (localized or generalized)	Anterior bulging of thorax	Total
5- 8 yrs.	4 (16%)	8 (32%)	25
8-12 yrs.	11 (17%)	20 (31%)	65
12-16 yrs.	10 (22%)	16 (43%)	47
Total	25 (18%)	44 (32%)	137

Duration of QRS Complex

The duration of the QRS complex was significantly prolonged in asthmatic children as compared with normal children (table 7), although there were a number of individual exceptions. Myers and his associates[19] stated that when QRS duration was compared with

Table 10

Electrocardiographic Orientation of the Heart

Cases	Vertical	Semi-vertical	Inter-mediate	Semi-horizontal	Horizontal	Total no.
Asthmatic children in this series	94 (68%)	35 (26%)	5 (3%)	2 (2%)	1 (1%)	137 (100%)
Normal children studied by Goodwin	21 (40%)	—	29 (55%)	—	3 (5%)	52 (100%)

heart weight, a trend was found toward slightly longer QRS duration with increasing weight, even though no close correlation could be made. It can, therefore, reasonably be concluded that the ventricular mass of the adolescent asthmatic patient is increased as compared with the normal.

Heart Rate and Duration of P-R and Q-T Intervals

Heart rates were increased in the older asthmatic age groups (table 8), but the clinical significance of this finding is not clear. Although the duration of P-R and Q-T intervals became longer with increasing age in both asthmatic and normal children, there was no significant difference between the 2 groups.

Electrocardiographic Position of the Heart

In 1952 Goodwin[18] charted the electrocardiographic position of the heart in 53 healthy children from 16 months to 15 years in age. The heart assumed the intermediate position in 29 cases (55 per cent), vertical position in 21 cases (40 per cent), and horizontal position in 3 cases (5 per cent). There was a great discrepancy between these cases and our asthmatic children (table 10).

The asthmatic child thus has a much greater tendency toward a vertical heart, perhaps associated with the displacement of the diaphragm resulting from early emphysema.

Summary

Electrocardiograms of 137 asthmatic children, 5 to 16 years in age, were compared with findings in normal children.

The following deviations from normal were found: lower voltage and longer duration of P waves in all leads; lower voltage of R waves in all precordial leads and almost all limb and unipolar leads; deeper S waves over left precordial leads; slight delay of intrinsicoid deflection in right precordial leads, but no difference in left precordial leads; somewhat increased duration of QRS complexes; increased heart rate in the older age groups, but no differences in P-R and Q-T intervals; predominantly vertical electrocardiographic position of the heart.

These observations provide further electrocardiographic evidence that asthmatic children, compared with normal children of the same age range, show a tendency toward right ventricular hypertrophy and hyperinflated lungs.

Summario in Interlingua

Le electrocardiogrammas de 137 juveniles asthmatic de 5 a 16 annos de etate esseva comparate con observationes in juveniles normal.

Le sequente deviationes ab le norma esseva trovate in le asthmaticos: Un plus basse voltage e un plus longe duration del unda P in omne le derivationes; un plus basse voltage del unda R in omne le derivationes precordial e in quasi omne le derivationes extremital e unipolar; un plus basse unda S super le derivationes sinistro-precordial; un leve retardo del deflexion intrinsecoide in le derivationes dextero-precordial sed nulle differentia in le derivationes sinistro-precordial; un leve augmento in le duration del complexo QRS; un plus alte frequentia cardiac in le gruppos de etate plus matur sed nulle differentia in le intervallos P-R e Q-T; e un position electrocardiographic del corde de character predominantemente vertical.

Iste constatationes provide un prova electrocardiographic additional que juveniles asthmatic—in comparation con juveniles normal del mesme etate general—manifesta un tendentia de disveloppar hypertrophia ventricular e pulmones hyperinflate.

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AHA Scientific Sessions Program

Six sessions of broad clinical interest will be held again during the American Heart Association's annual Scientific Sessions in Kiel Auditorium, St. Louis, October 21-23. The American Academy of General Practice has classified these sessions as acceptable for Category II credit for members.

The six clinical programs, to run concurrently with the special scientific sessions, will stress the practical application of findings in cardiovascular research. They will be proportioned among symposia, panels, lectures of general interest and submitted papers on recent results of investigations.

Aortic and Coronary Atherosclerosis in the Three Racial Groups in Cape Town

By M. I. Sacks, M.B., Ch.B., M.Med. (Path.)

Interracial differences in the prevalence of coronary heart disease in various parts of the world have aroused great interest in recent years. Among the many studies of the multiracial population of the African continent have been several indicating a considerable difference in the incidence of the clinical manifestations of coronary vascular disease in the 3 racial groups constituting the population of Cape Town. Studies on patients attending the Groote Schuur Hospital have shown that electrocardiographic evidence of myocardial infarction and ischemic heart disease is very uncommon in the Bantu and more common in the whites than in the Cape Coloured.[1, 2] A low incidence of myocardial infarction in a particular racial group suggests but does not necessarily prove that atherosclerosis is less severe in that group, and the results of clinical studies do not necessarily reflect the frequency and severity of subclinical atherosclerosis. This study is an attempt to see if there are comparable differences in the incidence and severity of atherosclerosis at autopsy.

The socioeconomic and dietary background of the 3 racial groups in Cape Town has been discussed by Bronte-Stewart et al.[3] The Bantu usually occupy the lowest socioeconomic plane, whereas the Cape Coloured form an intermediate group between the Bantu and whites.

Material and Methods

Over a 5-year period (October 1953 to September 1958) material from 1,250 unselected adult autopsies performed in the Department of Pathology of the University of Cape Town was personally examined. Natural illness was the cause of death in all cases. In 1,180 cases, both aorta and coronary arteries were examined. In 53 additional cases the coronary arteries were studied but the aorta was excluded because of the presence of syphilitic aortitis (19 cases) or more often because the entire aorta had not been preserved. In 17 cases only the aorta was available. There is no reason to believe that there was any racial bias in the exclusion of either the aorta or coronary arteries in these 70 cases except that there were more cases of syphilitic aortitis among the Cape Coloured and Bantu than among the whites.

With few exceptions the autopsy material was drawn from the Groote Schuur Hospital. This is an 854-bed general hospital serving the population of Cape Town and the surrounding districts. The population admitted to the hospital is selected in that a means test restricts attendance to the poorer section of the community. All the Bantu, almost all the Cape Coloured, but only the poorer whites are eligible for admission. During the period under review there were 5,665 deaths in patients of all ages in the Groote Schuur Hospital of whom 11 per cent were Bantu and the remainder approximately evenly divided between whites and Cape Coloured. Our autopsy material is representative of the 3 racial groups except that permission for autopsy is refused on religious grounds in the Moslem section of the coloured community (Cape Malays).

There were unfortunately relatively few Bantu over the age of 60 and few Bantu females. There were more Cape Coloured than whites in the younger age groups, whereas the reverse applied over the age of 50. As the incidence of severe atherosclerosis varies with age it has been necessary to divide the series into age groups by decade for purposes of interracial comparison, and this has unfortunately resulted in many of the groups becoming too small for satisfactory statistical analysis.

In a small percentage of the cases the autopsy was performed by the author and the lesions were graded at the time of autopsy. In the great majority, however, the aorta and the heart were first seen after overnight preservation in the refrigerator, and the lesions were classified by the author without knowledge of the race, sex, or age of the patient. The aorta and coronary arteries were separately classified in each case.

Coronary Arteries

Although the degree of luminal narrowing produced by atherosclerosis is best assessed from the

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ppearance of the vessels in cross-section, the umber of plaques is best evaluated in vessels pened longitudinally. In the present study the oronary arteries were always opened along their ain branches and plaques were classified as beg few, moderate, or numerous. This was obviusly an arbitrary method of grading but the maority of cases could readily be classified. Where oubt existed as to which of two possible desigations applied, the worse grading was selected. lthough it was realized that the method used to isplay the vessels was not a really satisfactory ay of assessing the degree of narrowing, a record as also kept of whether the opened vessels appeared to be significantly narrowed by the atheromatous plaques. We thought that we were at least able to identify those cases in which luminal narowing was undoubtedly severe and also those ases in which there was very little or no narrowing. Each of the main coronary arteries was finally classified into 1 of 4 grades:

Grade 1. No lesions or fatty streaking without actual plaque formation.

Grade 2. Mild coronary atherosclerosis. Few plaques with little or no narrowing.

Grade 3. Moderate coronary atherosclerosis. Moderate number of plaques but without severe luminal narrowing.

Grade 4. Severe coronary atherosclerosis. Numerous plaques present irrespective of the degree of narrowing, or severe narrowing present irrespective of the number of plaques. The phrase "severe coronary atherosclerosis" has been applied to any case that was classified as showing grade 4 lesions. The phrase "severe luminal narrowing" has been used for those severe cases that were severe by virtue of severe narrowing, irrespective of the number of plaques present.

The left and right coronary arteries were graded separately and the worse grading has been used in each case.

Aorta

The opened aorta was examined from the valve ring to the bifurcation. The number and character of the atherosclerotic lesions were recorded in each of the following 4 segments: (i) Ascending aorta and aortic arch; (ii) Descending thoracic aorta; (iii) Abdominal aorta down to 2 to 3 inches above the aortic bifurcation; (iv) The region of the ortic bifurcation.

We were more interested in gross lesions than in early fatty streaking, so that sudanophilic staining of the aorta was not carried out, and cases showing no lesions have been classified together with those showing fatty streaking for the purposes of this presentation. More attention was paid to the number of lesions than to the presence or absence of complications such as ulceration, thrombosis, and calcification in assigning a grading to a particular case. Because of the subjective nature of the appraisal it was considered that the simpler the classification, the less would be the difficulty in assigning a case to a particular group and the more reproducible would be the assessment from day to day. Each aortic segment was therefore assigned to one of the following groups:

Grade 1. No lesions or superficial fatty streaking. Cases showing occasional small punctate yellow spots that were barely raised above the surface (so-called lipid spots) were also included in this category.

Grade 2. Mild atherosclerosis. Definite, raised, pearly white or yellow plaques present but few in number and quite discrete. Ulceration or calcification was very uncommon in this group but a case that would otherwise have been classified here was not excluded if an occasional lesion was complicated by ulceration or calcification.

Grade 3. Moderate atherosclerosis. Plaques more numerous than in grade 2 but still discrete. Usually no ulceration or calcification but the presence of these complications did not preclude classification in this group.

Grade 3A. Moderate atherosclerosis. Numerous plaques becoming confluent but obviously superficial and without ulceration or calcification. This group was separated from grade 4 as, although the lesions were numerous, they were so obviously more superficial and less raised than those classified as grade 4. Sometimes the lesions in this group appeared to be hardly more than a confluent streaking. This type of case was not common and has arbitrarily been classified with the cases of moderate rather than severe atheroma.

Grade 4. Severe atherosclerosis. Numerous plaques becoming confluent or actually lining whole segments of the aortic wall. Usually associated with complications such as ulceration or calcification, or both. A case with numerous lesions but no ulceration or calcification was also included in this category unless the lesions were obviously superficial in type, in which case it was classified as grade 3A.

In the comparison of findings in the 3 racial groups each case was graded according to the worst aortic segment.

Results

Coronary Atherosclerosis in Men

Table 1 shows the frequency of the various grades of atherosclerosis in men in the 3 racial groups.

Under the age of 40 years severe (grade 4) coronary atherosclerosis was rare but occasional cases were encountered in both Cape Coloured and whites.

Table 1

Coronary Atherosclerosis in Men

Age group	Race	No. of cases	Grade of coronary atherosclerosis* 1	2	3	4	Severe luminal narrowing
20 — 29	White	15	27 (4)	46 (7)	27 (4)	0	0
	Cape Coloured	28	50 (14)	35 (10)	11 (3)	4 (1)	4 (1)
	Bantu	16	87 (14)	13 (2)	0	0	0
30 — 39	White	16	19 (3)	44 (7)	31 (5)	6 (1)	6 (1)
	Cape Coloured	37	51 (19)	24 (9)	22 (8)	3 (1)	0
	Bantu	21	62 (13)	33 (7)	5 (1)	0	0
40 — 49	White	43	5 (2)	30 (13)	26 (11)	39 (17)	28 (12)
	Cape Coloured	51	12 (6)	29 (15)	41 (21)	18 (9)	8 (4)
	Bantu	37	62 (23)	16 (6)	16 (6)	6 (2)	0
50 — 59	White	82	7 (6)	16 (13)	42 (34)	35 (29)	23 (19)
	Cape Coloured	59	5 (3)	29 (17)	42 (25)	24 (14)	14 (8)
	Bantu	23	48 (11)	17 (4)	31 (7)	4 (1)	0
60 — 69	White	110	2 (2)	15 (16)	29 (32)	54 (60)	38 (42)
	Cape Coloured	55	19 (11)	2 (1)	44 (24)	35 (19)	22 (12)
	Bantu	9	56 (5)	22 (2)	0	22 (2)	0
70 plus	White	89	2 (2)	10 (9)	24 (21)	64 (57)	42 (37)
	Cape Coloured	27	7 (2)	15 (4)	33 (9)	45 (12)	15 (4)
	Bantu	10	50 (5)	20 (2)	10 (1)	20 (2)	0

*The incidence of the various grades is given as a percentage. The figure in parentheses denotes the number of cases in each grade.

Severe coronary atherosclerosis was less common in the Bantu than in the whites in each age group over 40 years. The difference was most marked in the fifth ($p < 0.01$) and sixth ($p < 0.05$) decades. Only 3 (5 per cent) of 60 Bantu men in the fifth and sixth decades showed severe coronary atherosclerosis as compared to 46 (37 per cent) among 125 whites. There were unfortunately few Bantu over the age of 60 in the series. They too showed a lower incidence of grade-4 lesions than the whites but the difference is not statistically significant. Of great interest is the fact that the relatively few cases of severe coronary atheroma encountered in Bantu subjects, even in the older age groups, were so classified because of the number of plaques present, and the degree of narrowing was usually slight or at most moderate. Grade-3 lesions (moderate coronary atherosclerosis) were also less common in the Bantu, and the coronary arteries of the Bantu often showed no lesions or merely a few fatty streaks in age groups in which it was rare to see freedom from atheroma in whites. Between the ages of 40 and 59 more than half of the Bantu men but only 6 per cent of the white men showed no more than slight fatty streaking. The coronary arteries of 10 of the 19 Bantu men over the age of 60 showed no intimal lesions or mild fatty streaking and a similar degree of freedom from atheroma was exceedingly rare (4 out of 199 cases) in whites over this age.

In each decade over the age of 40 severe coronary atheroma was also less common in the Cape Coloured than in the whites but the differences were less marked than those between the Bantu and the whites. In the fifth decade the difference between Cape Coloured and whites is probably statistically significant ($p < 0.05$). This lower incidence of severe coronary atherosclerosis in the Cape Coloured is not statistically significant in the sixth, seventh, and eighth decades considered individually, but in these 3 age groups together it is significant at the 5 per cent level. Unlike the Bantu, the Cape Coloured did show severe luminal narrowing but less commonly than the whites, especially in the fifth decade. Not only was there less difference between the incidence of severe coronary atherosclerosis in the whites and Cape Coloured than in the whites and Bantu, but grade-3 lesions were encountered as commonly in the Cape Coloured as in the whites or even more commonly. Under the age of 40 it was more

Table 2

Coronary Atherosclerosis in Women

Age group	Race	No. of cases	Grade of coronary atherosclerosis* 1	2	3	4	Severe luminal narrowing
20 — 29	White	16	57 (9)	31 (5)	6 (1)	6 (1)	0
	Cape Coloured	30	60 (18)	33 (10)	7 (2)	0	0
	Bantu	11	82 (9)	9 (1)	9 (1)	0	0
30 — 39	White	10	20 (2)	60 (6)	20 (2)	0	0
	Cape Coloured	47	49 (23)	36 (17)	9 (4)	6 (3)	2 (1)
	Bantu	12	50 (6)	42 (5)	8 (1)	0	0
40 — 49	White	34	21 (7)	44 (15)	26 (9)	9 (3)	9 (3)
	Cape Coloured	53	25 (13)	38 (20)	26 (14)	11 (6)	8 (4)
	Bantu	18	61 (11)	28 (5)	11 (2)	0	0
50 — 59	White	65	17 (11)	28 (18)	26 (17)	29 (19)	22 (14)
	Cape Coloured	37	8 (3)	22 (8)	32 (12)	38 (14)	8 (3)
	Bantu	10	50 (5)	30 (3)	20 (2)	0	0
60 — 69	White	49	2 (1)	12 (6)	31 (15)	55 (27)	33 (16)
	Cape Coloured	28	7 (2)	21 (6)	47 (13)	25 (7)	14 (4)
	Bantu	5	20 (1)	20 (1)	20 (1)	40 (2)	0
70 — 79	White	62	2 (1)	8 (5)	26 (16)	64 (40)	34 (21)
	Cape Coloured	18	0	28 (5)	11 (2)	61 (11)	22 (4)

*The incidence is given as a percentage. The figure in parentheses denotes the number of cases.

common to find coronary arteries free or virtually free of atheroma in the Cape Coloured than in the whites, but over this age such freedom from atheroma was almost equally as uncommon in a Cape Coloured as in a white man.

Coronary Atherosclerosis in Women

The frequency of the various grades of coronary atherosclerosis in women in the 3 racial groups is shown in table 2.

Severe coronary atherosclerosis was rare in women under the age of 50, and the occasional white and Cape Coloured subjects who showed severe coronary atheroma at this age were almost invariably hypertensive. The absence of severe coronary atheroma in the small group of Bantu women under the age of 50 has no special significance in view of the rarity of severe lesions in the other racial groups below this age. It is, however, probably significant ($p < 0.05$) that a higher proportion of the Bantu women between the ages of 40 and 49 years showed complete freedom from coronary atheroma than did the whites or Cape Coloured. We cannot draw any definite conclusions about the incidence of coronary atherosclerosis in Bantu women over the age of 50 years, as so few elderly subjects were seen. It is, however, interesting that of the 10 cases in the sixth decade 5 showed no atheromatous plaques in the coronary arteries and none showed severe lesions. The coronary arteries of 2 of the 5 Bantu women over the age of 60 were classified as severe by virtue of the number of plaques present but in neither case was there severe luminal narrowing.

There was no constant difference in the incidence of severe coronary atherosclerosis between Cape Coloured and white women in the various age groups over the age of 50. Grade-4 lesions were slightly more common in the Cape Coloured in the sixth decade, more common in the whites in the seventh decade, and of approximately equal incidence in the 2 racial groups over the age of 70. Severe luminal narrowing did, however, appear to be less common in the Cape Coloured even in the sixth decade. This lower incidence of severe luminal narrowing in the Cape Coloured is not statistically significant but the trend appears to be consistent. It was uncommon to find coronary arteries completely free of atheroma in Cape Coloured or white women over the age of 50, and the Cape Coloured showed no greater freedom than the whites in this respect.

Table 3

Aortic Atherosclerosis in Men

Age group	Race	No. of cases	Grade of aortic atherosclerosis* 1	2	3 (and 3A)	4
20 — 29	White	16	44 (7)	50 (8)	6 (1)	0
	Cape Coloured	26	50 (13)	42 (11)	8 (2)	0
	Bantu	16	87 (14)	13 (2)	0	0
30 — 39	White	15	0	53 (8)	40 (6)	7 (1)
	Cape Coloured	38	34 (13)	50 (19)	16 (6)	0
	Bantu	22	36 (8)	54 (12)	5 (1)	5 (1)
40 — 49	White	40	0	15 (6)	27 (11)	58 (23)
	Cape Coloured	44	2 (1)	43 (19)	25 (11)	30 (13)
	Bantu	35	26 (9)	51 (18)	17 (6)	6 (2)
50 — 59	White	80	1 (1)	7 (6)	23 (18)	69 (55)
	Cape Coloured	55	0	24 (13)	22 (12)	54 (30)
	Bantu	23	26 (6)	39 (9)	17.5 (4)	17.5 (4)
60 — 69	White	109	1 (1)	3 (3)	10 (11)	86 (94)
	Cape Coloured	55	6 (3)	7 (4)	27 (15)	60 (33)
	Bantu	8	50 (4)	25 (2)	0	25 (2)
70 plus	White	85	0	2 (2)	4 (3)	94 (80)
	Cape Coloured	26	0	4 (1)	15 (4)	81 (21)
	Bantu	8	0	37.5 (3)	25 (2)	37.5 (3)

*The incidence is given as a percentage. The figure in parentheses denotes the number of cases in each grade.

Aortic Atherosclerosis in Men

Table 3 shows the frequency of the various grades of aortic atherosclerosis in the 3 racial groups.

No cases of severe aortic atheroma were encountered under the age of 30 years. Young Cape Coloured and white men in the third decade quite often showed mild atherosclerosis, whereas the Bantu usually showed no lesions or merely fatty streaking.

In the fourth decade 1 case of severe aortic atheroma was encountered in a white and 1 in a Bantu; both these subjects were hypertensive. Moderate atheroma (grades 3 and 3A) was more common in the whites in this decade than in the Cape Coloured or Bantu, most of whom showed either mild atheroma or fatty streaking.

Over the age of 40 the incidence of severe aortic atheroma increased with age in each of the 3 racial groups. In each decade the incidence remained lower in the Bantu than in the whites or Cape Coloured. The difference in the incidence of severe aortic atheroma between the whites and Bantu is statistically significant in the fifth decade ($p < 0.001$) and in the sixth decade ($p < 0.01$). Satisfactory interracial comparison in the older age groups is prevented by the small number of Bantu subjects. It is, however, noteworthy that although one third (5 out of 16 cases) of the small group of Bantu men over the age of 60 showed severe aortic atheroma the comparable incidence in whites was in the neighborhood of 90 per cent (174 of 194 cases). There was also a lower incidence of moderate aortic atheroma in the Bantu, who more often showed no or minimal lesions, than the whites. Between the ages of 40 and 59 years, 15 of 58 aortas of the Bantu showed no more than fatty streaking, whereas only 1 of 120 aortas of the whites showed this freedom from atherosclerosis. Even over the age of 60 years it was not uncommon to find the aorta of a Bantu subject showing no or very few atheromatous plaques.

The differences in the frequency of severity of aortic atheroma between the whites and Cape Coloured subjects were much less marked than those between the whites and Bantu. Severe aortic atheroma was encountered slightly less frequently in the Cape Coloured than in the whites over the age of 40, but the differences are not statistically significant in any individual age group. The tendency for a slightly lower incidence of severe lesions in the Cape Coloured was consistent, and in the 4

Table 4

Aortic Atherosclerosis in Women

Age group	Race	No. of cases	Grade of aortic atherosclerosis* 1	2	3 (and 3A)	4
20 — 29	White	16	75 (12)	19 (3)	6 (1)	0
	Cape Coloured	29	69 (20)	21 (6)	7 (2)	3 (1)
	Bantu	11	55 (6)	36 (4)	9 (1)	0
30 — 39	White	10	40 (4)	50 (5)	0	10 (1)
	Cape Coloured	47	32 (15)	45 (21)	17 (8)	6 (3)
	Bantu	12	50 (6)	25 (3)	17 (2)	8 (1)
40 — 49	White	33	3 (1)	43 (14)	27 (9)	27 (9)
	Cape Coloured	53	15 (8)	41 (22)	25 (13)	19 (10)
	Bantu	16	31 (5)	50 (8)	13 (2)	6 (1)
50 — 59	White	65	1.5 (1)	14 (9)	23 (15)	61.5 (40)
	Cape Coloured	36	6 (2)	17 (6)	25 (9)	52 (19)
	Bantu	10	10 (1)	60 (6)	20 (2)	10 (1)
60 — 69	White	49	0	8 (4)	6 (3)	86 (42)
	Cape Coloured	27	4 (1)	11 (3)	22 (6)	63 (17)
	Bantu	5	0	0	40 (2)	60 (3)
70 plus	White	59	0	3 (2)	7 (4)	90 (53)
	Cape Coloured	18	0	6 (1)	33 (6)	61 (11)

*The incidence is given as a percentage. The figure in parentheses denotes the number of cases in each grade.

age groups together is significant at the 5 per cent level. Although Cape Coloured men over the age of 40 did appear to show a slightly lower incidence of severe atheroma than the whites, they showed moderate atheroma as commonly or, over the age of 60, more commonly than the whites, and the Cape Coloured men over the age of 40 were really no more likely than the whites to show complete freedom from aortic atheroma.

Aortic Atherosclerosis in Women

The frequency of the various grades of aortic atherosclerosis in women is shown in table 4.

Occasional cases of severe aortic atherosclerosis were encountered in women under the age of 40 years in each of the 3 racial groups. Thereafter the incidence of severe lesions increased with age as in men. In the fifth decade severe atheroma was more common in white men than in white women and slightly more common in Cape Coloured men than in Cape Coloured women but this sex difference was not apparent in the older age groups.

There were too few Bantu women for satisfactory interracial comparison. The occurrence of severe aortic atheroma in only 1 of 16 Bantu women in the fifth decade (as compared to 9 of 33 whites), and in only 1 out of 10 cases in the sixth decade (as compared to 40 out of 65 whites) certainly suggests that severe aortic atheroma is less common than in the whites. The fact that 3 of the 5 Bantu women over the age of 60 showed severe aortic atheroma does not necessarily invalidate this suggestion, as these 3 cases were all hypertensive and so formed not only a small but also a rather select group.

In each decade over the age of 40 years severe aortic atheroma was encountered in a slightly higher percentage of white than Cape Coloured women but the differences are not statistically significant. The results in table 4 also suggest that the more moderate degrees of aortic atheroma were as common, or even more common, in Cape Coloured women than in white women, and that freedom from atheroma or the presence of only mild atheroma was as infrequent in elderly Cape Coloured women as in elderly white women.

Distribution, Extent, and Character of the Lesions in Cases of Severe Aortic Atherosclerosis

There did not appear to be any difference between the 3 racial groups of either sex in the localization of severe aortic lesions. Severe aortic atherosclerosis was more common in the

abdominal than the thoracic portion of the aorta, and the bifurcation was usually the most affected portion. In the fifth and sixth decades, approximately one third of the severe cases in both whites and Cape Coloured showed the lesions to be confined to the bifurcation and in only one third did they involve at least 3 of the 4 segments of the aorta. Over the age of 60, however, the majority of the cases with severe lesions showed involvement of at least 3 of the 4 aortic segments and the proportion of the severe cases showing this widespread involvement was as high in the Cape Coloured as in the whites. There were only 18 cases of severe aortic atherosclerosis in Bantu subjects and in half of these the severe lesions involved the greater part of the aorta.

We have graded as severe aortic atherosclerosis those cases in which numerous lesions were present, irrespective of the presence or absence of complications such as ulceration or calcification, unless the lesions were obviously superficial. In most of the severe cases complicated lesions were present, especially near the bifurcation and in less than 5 per cent of the severe cases in white men, white women, and Cape Coloured men were the lesions uncomplicated. In contrast, 16 per cent of the Cape Coloured women with severe aortic atheroma were free of ulceration or calcification. A similar trend was noted in the Bantu, and in 4 of the 18 cases of severe aortic atherosclerosis the lesions were uncomplicated. In no Bantu cases did we observe the very marked degrees of ulceration and calcification that are sometimes seen in white and Cape Coloured subjects.

Effect of Hypertension on the Frequency and Severity of Atherosclerosis

Our findings support the general belief that the presence of systemic hypertension contributes to the development and severity of atherosclerosis, and it is of interest to evaluate the effect of hypertension in each of the 3 racial groups. A basic difficulty in an autopsy series is in deciding whether or not hypertension has been present. Satisfactory clinical readings were not always available, and many of the patients were admitted in a shocked or terminal state. Left ventricular hypertrophy, in the absence of any other known cause, is probably the best single indication at autopsy that the patient has been hypertensive for at least some time before death, although claims have been made that occlusive coronary artery disease can cause myocardial hypertrophy in the absence of hypertension.[4, 5] We have accepted as hypertensive only those cases in which undoubted left ventricular hypertrophy was accompanied by clinical evidence of hypertension (a blood pressure reading of at least 160/100 mm. Hg). The evaluation of nonhypertensive cases was similarly based on the absence of left ventricular hypertrophy and of hypertensive blood pressure readings. There remained a group in which no definite conclusion about hypertension was possible, and these we labeled as doubtful.

Figure 1 shows the incidence of hypertension in cases over the age of 39 in the 3 racial groups. The incidence of cases that fell into the doubtful group is also shown, and it is apparent that the proportion of such cases was rather high, especially in the older age groups.

There was little difference in the incidence of hypertension in the Cape Coloured and white men, except over the age of 70, where the higher incidence in the whites was largely neutralized by a higher percentage of doubtful cases among the Cape Coloured. Hypertension was no less common in the Bantu men than in the whites or the Cape Coloured, except that there were no hypertensive cases among the small group of Bantu men in the seventh decade. The number of doubtful cases was, however, rather higher in the whites and Cape Coloured than in the Bantu in some age groups.

In women there was little difference between the whites and the Cape Coloured, except in the sixth decade, in which hypertension was more than twice as common in the Cape Coloured. Bantu women had approximately the same incidence of hypertension as did the

Cape Coloured women, and 4 of the 5 cases in the seventh decade were hypertensive.

Table 5 shows the frequency of severe (grade 4) coronary atherosclerosis in hypertensive and nonhypertensive subjects in the fifth to seventh decades in Cape Coloured and whites. The findings recorded in this table are interesting but must be interpreted with caution as the subdivided groups are small ones. In both racial groups severe coronary atherosclerosis was apparently more frequent in hypertensive than in nonhypertensive subjects of the same age and sex. The effect of hypertension was best seen in the fifth decade and was rather more obvious in women than in men. If one considers only the hypertensive cases the differences between the whites and Cape Coloured men become less evident. The findings in table 5 also suggest that a higher incidence of hypertension may explain the slightly higher incidence of severe coronary atheroma in Cape Coloured than white women in the sixth decade in the whole series.

Many of the Bantu age groups are unfortunately too small for a separate consideration of the hypertensive and nonhypertensive cases. As in the whites and Cape Coloured the hypertensive Bantu subjects appeared to show a more severe degree of coronary atheroma than nonhypertensive Bantu of the same age. Five of the 9 Bantu patients with severe and 16 of the 22 with moderate coronary atherosclerosis in the whole series were hypertensive.

Table 6 shows the grade of coronary atherosclerosis in hypertensive and nonhypertensive Bantu and white men between the ages of 40 and 59. Severe and moderate degrees of coronary atheroma were more common in hypertensive than nonhypertensive subjects in both racial groups. In 11 of the 15 hypertensive but in only 4 of the 43 nonhypertensive Bantu men in this age group was there more than mild coronary atheroma. Severe coronary lesions were more frequent in hypertensive whites than in the hypertensive Bantu, and severe luminal narrowing was not encountered in the Bantu, even in the presence of hypertension.

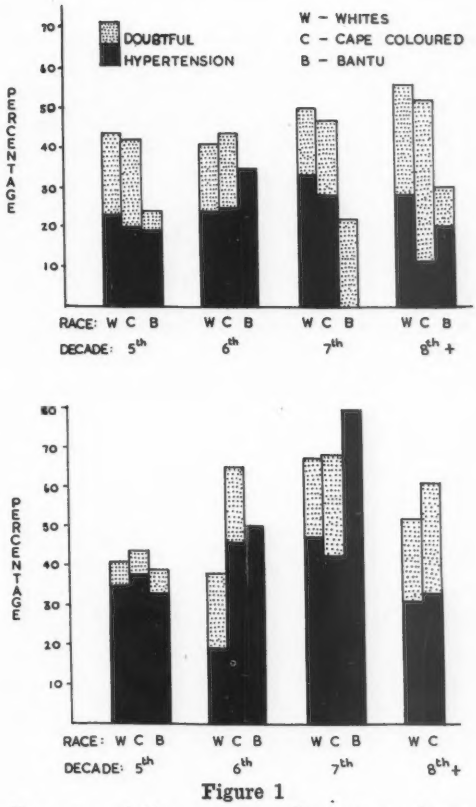

Figure 1

Top, *men;* bottom, *women. Percentage of cases showing clinical and pathologic evidence of hypertension, and percentage of cases in which hypertensive status was doubtful on the data available.*

The aggravating effect of systemic hypertension on aortic atherosclerosis was seen in both Cape Coloured and whites below the age of 50 and was rather more pronounced in the Cape Coloured than in the whites, and in women than in men. Not surprisingly the effect of hypertension on aortic atherosclerosis was not as evident in the older age groups, particularly in whites in whom severe aortic lesions were very common, even in the absence of hypertension. Of the 18 Bantu cases of severe aortic atherosclerosis in the whole series 10 were hypertensive.

Incidence of Diabetes Mellitus

There were few known diabetic men of any of the racial groups or diabetic Bantu women.

Table 5

Incidence of Severe Coronary Atherosclerosis in Hypertensive and Nonhypertensive Subjects

	Fifth decade		Sixth decade		Seventh decade	
	White	Cape Coloured	White	Cape Coloured	White	Cape Coloured
Men						
Hypertensive	80 (8)	40 (4)	40 (8)	40 (6)	70 (25)	60 (9)
Nonhypertensive	23 (5)	10 (3)	29 (14)	18 (6)	40 (22)	17 (5)
p	0.01	0.05	Nonsignif.	Nonsignif.	Nonsignif.	<0.05
Women						
Hypertensive	25 (3)	29 (6)	50 (6)	65 (11)	66 (16)	50 (6)
Nonhypertensive	0	0	17 (7)	16 (2)	33 (5)	0
p	<0.05	<0.01	<0.05	<0.05	Nonsignif.	<0.05

The incidence of severe atherosclerosis is given as a percentage. The figure in parentheses denotes the number of cases of severe atherosclerosis.

The over-all incidence of diabetes was much the same in the white and Cape Coloured women (12.6 per cent and 13.3 per cent respectively), but the incidence was rather higher in Cape Coloured women in the fifth and sixth decades and in white women in the seventh decade. The slightly higher incidence of severe coronary atheroma in Cape Coloured women in the sixth decade and in white women in the seventh decade still persisted, however, if the diabetic cases were excluded.

Autopsy Incidence of Myocardial Infarction in the Three Racial Groups

Myocardial infarction associated with atherosclerosis was rarely encountered under the age of 40 in this autopsy series.

Table 7 shows the incidence of recent or healed myocardial infarction in the coloured and whites over the age of 40 years in this series of 1,250 cases, and also in a larger series of 2,509 consecutive adult autopsies performed in the Department of Pathology of the University of Cape Town during the years 1951 to 1958. Occasional cases of myocardial infarction, which were obviously not associated with atherosclerosis (e.g., cases due to coronary embolism, polyarteritis nodosa, or syphilitic involvement of the coronary ostia), have been excluded from this table.

In both the smaller and larger series of cases myocardial infarction was more common in white men than in Cape Coloured men in each age group. The differences are not statistically significant in all the individual age groups, especially in the smaller series of 1,250 cases, but the trend is consistent and the difference is significant at the 1 per cent level if the 4 age groups are considered together.

Myocardial infarction was uncommon in both white and Cape Coloured women under the age of 50. Over the age of 50 the incidence of myocardial infarction was higher in white than in Cape Coloured women in each age group. The differences are not, however, statistically significant except in the sixth decade.

It did at first seem that in certain age groups, particularly in the sixth decade, the difference in the incidence of myocardial infarction between white and Cape Coloured patients was greater than the difference in the incidence of severe coronary atheroma. The difference in the incidence of myocardial infarction in white and Cape Coloured men in the sixth decade is, however, rather less impressive in the large autopsy series analyzed in table 7 than it was in the smaller series whose coronary arteries were studied. It is of interest that although Cape Coloured women had a slightly higher incidence of severe coronary atheroma than white women in the sixth decade they had a lower incidence of myocardial infarction. They did, however, also show a lower incidence of severe luminal narrowing than the whites, and for this reason one hesitates to ascribe undue significance to the apparent discrepancy between the incidence of

Table 6

Coronary Atherosclerosis in Hypertensive and Nonhypertensive White and Bantu Men between the Ages of Forty and Fifty-nine Years

	Total no. of cases	Percentage incidence of various grades of coronary atherosclerosis			
		Grade 1	Grade 2	Grade 3	Grade 4
Hypertensive Bantu	15	27	0	60	13
Nonhypertensive Bantu	43	68	23	7	2
Hypertensive whites	30	3	0	44	53
Nonhypertensive whites	72	9	29	36	26

severe coronary atheroma and of myocardial infarction.

There were 2 cases of myocardial infarction in Bantu subjects in our series of 1,250 cases and 2 further cases among the 309 Bantu subjects in the larger autopsy series. In none of the 4 Bantu cases did the myocardial infarction appear to be the result of coronary atherosclerosis. Two of the cases have been described in detail by Schrire and Uys.[6] The third case was a Bantu man of 55 with a cardiac aneurysm presumed to be due to an old infarct but according to the autopsy protocols the coronary arteries were remarkably free of atheroma. The fourth case was a man of 28 years with chronic rheumatic heart disease, bacterial endocarditis, and no coronary atheroma.

Discussion

The method of grading that we have used is, like all subjective methods of appraisal, subject to certain limitations. We believe, however, that it is capable of yielding reasonably consistent results, at least in the hands of one observer, and that it has provided a satisfactory and practical way of directly comparing the frequency and severity of atherosclerosis in the 3 racial groups.

It is not easy to compare our results with those of other workers, as different standards for grading severity may have been used and as a clear distinction has not always been drawn by others between the coronary arteries and the aorta. Our findings in the Bantu are in accord with those of pathologists and clinicians in many parts of Africa, whose experience has been that severe coronary atherosclerosis is uncommon and myocardial infarction very rare in the Bantu. Higginson and Pepler[7] concluded that severe aortic and coronary atherosclerosis were less common at autopsy in the hospitalized Bantu in Johannesburg than among comparable groups in the Danish and American hospital populations. Hannah's study,[8] reported from Northern Rhodesia, is of particular interest as the same pathologist compared the necropsy findings in small groups of whites and Bantu. He concluded that the Bantu, while not entirely immune to atherosclerosis developed it much less frequently than the whites and rarely died of its complications.

One group of workers has, however, recently questioned the Bantu's freedom from atherosclerosis. Laurie and Woods[9] discussed the autopsy incidence of aortic atherosclerosis and of cerebral hemorrhage in the Bantu in Durban, South Africa. They were of the opinion that their findings and those of Becker[10] provided enough evidence to refute the view that the Bantu enjoy any relative freedom from atherosclerosis or its complications. It is important to stress at the outset that their report and that of Becker dealt with aortic and not coronary atherosclerosis, and that any conclusions drawn from their studies cannot be applied to the problem of coronary atherosclerosis as some observers have apparently done.[11] We do not agree with the inferences that Laurie and Woods have themselves drawn from the incidence of cerebral hemorrhage in their series or with their interpretation of Becker's findings. We agree with them that cerebral hemorrhage is common in the Bantu but do not regard this as an indication of the frequency of atherosclerosis, as they have

Table 7

Incidence of Myocardial Infarction in Cape Coloured and Whites

Age group	Series	White men	Cape Coloured men	White women	Cape Coloured women
40 — 49	A*	20.9 (9)‡	9.8 (5)	5.9 (2)	3.6 (2)
	B†	17 (19)	6 (8)	5.7 (4)	3.6 (4)
50 — 59	A	15.9 (13)	1.6 (1)	12.3 (8)	2.7 (1)
	B	11.9 (19)	5.2 (7)	12.5 (12)	2.3 (2)
60 — 69	A	21.2 (24)	8.8 (5)	29.4 (15)	10.7 (3)
	B	19 (39)	7.4 (7)	19 (24)	13.1 (8)
70 plus	A	28.9 (26)	11.1 (3)	17.8 (11)	16.6 (3)
	B	26.8 (44)	17 (8)	20.1 (21)	11.1 (3)

*(A) Incidence in 1,250 cases comprising our series.

†(B) Incidence of 2,509 consecutive adult autopsies, 1951-1958.

‡The incidence is given as a percentage of the total number of autopsies. The figure in parentheses denotes the number of cases of infarction.

done. Cerebral hemorrhage in the Bantu, as in the whites, is usually the result of hypertension, and its frequency is not an index of the frequency of cerebral atherosclerosis. They quote Becker as having found severe aortic atherosclerosis in 26 per cent of Bantu over the age of 45. In actual fact Becker stated that aortic atheroma occurred in 56 per cent of Bantu over this age, and in 26 per cent of these cases with aortic atheroma were the lesions graded as severe.[10] From this it appears that only 14 per cent of Bantu over 45 showed severe aortic atheroma, an incidence that is surely well below that in the whites even allowing for differences in standards of grading.

Although our Bantu groups have been small, we have been able to compare them directly with the whites, an advantage not shared by most previous reports including that of Laurie and Woods. Severe aortic and coronary atherosclerosis were encountered far less commonly in Bantu men between the ages of 40 and 59 than in whites of the same age. Severe lesions seemed to be similarly less frequent in older Bantu men and in Bantu women but our material has been limited in this respect. Two important features that emerge from this study are the great rarity of severe luminal narrowing of the coronary arteries in the Bantu and the fact that the aorta and coronary arteries often show complete or virtually complete freedom from atherosclerosis in age groups in which it is rare to find such freedom in whites.

There are no previous autopsy reports of the frequency and severity of aortic and coronary atherosclerosis in the Cape Coloured. The differences between the white and Cape Coloured groups in our series were less striking than those between the whites and Bantu. Cape Coloured men did show less severe aortic and coronary atherosclerosis than white men but complete freedom from atherosclerosis was no more common than in the whites, except possibly in the third and fourth decades. Unlike the Bantu, the Cape Coloured men did show severe luminal narrowing of their coronary arteries but less commonly than the whites. Severe aortic atheroma was virtually as common in the Cape Coloured as in the white women. There was no constant difference between these 2 groups of women in the incidence of severe coronary atherosclerosis as judged by the number of plaques present, but severe luminal narrowing did appear to be less common in the Cape Coloured. It should again be pointed out that there was a particularly high incidence of hypertension in certain of the Cape Coloured women groups, and this may at least partly explain why the differences between white and Cape Coloured men appeared to be greater than those between white and Cape Coloured women in certain age groups.

There are several possible fallacies in infer-

ences drawn from autopsy studies on the relative frequency of severe atherosclerosis. The conclusions can apply only to the population at risk. There may be selective factors that determine why patients dying as a result of atherosclerosis or its complications are more likely to be admitted to the hospital in one than in another racial group. It has even been stated that the final illness may itself in some way modify the atherosclerotic process, although this is difficult to visualize. Our autopsy findings may well reflect more accurately the frequency of severe coronary atherosclerosis and myocardial infarction in the Cape Coloured and Bantu than in the whites. The general impression exists among physicians in Cape Town that the incidence of coronary artery disease in the white population is greater in cases seen in private than in hospital practice,[12] and it is very likely that the frequency of severe coronary atherosclerosis and myocardial infarction in whites in our autopsy material is lower than that in the total white population of Cape Town, as admission to Groote Schuur Hospital is restricted to the poorer members of the community.

The purpose of our investigation has been to provide data on the frequency of atherosclerosis in the 3 racial groups to add to that which already exists on the incidence of the disease based on clinical studies. We have not set out to prove or disprove any particular point with reference to the wider problem of the etiology of atherosclerosis. The many possible factors that may operate in determining the differences in the racial incidence of coronary artery disease have recently been reviewed by Brock and Gordon[13] and the relative importance of most of these cannot be assessed in an autopsy study. It is, however, clear that many factors must be taken into account when discussing the significance of a varying prevalence of atherosclerosis. The importance of the age distribution of the cases in the different racial groups is obvious, as is that of hypertension. The hypertensive factor must be evaluated separately for each group. The lower frequency of severe atherosclerosis in the Bantu cannot be attributed to a lower incidence of hypertension. At the same time the fact that the Bantu commonly develop hypertension but uncommonly show severe atherosclerosis should not be used as an argument minimizing the effect of hypertension on the development of atherosclerosis. It is true that in the presence of hypertension the Bantu still show less atherosclerosis than the whites, but it is also true that the hypertensive Bantu show more atherosclerosis than the nonhypertensive Bantu. In the presence of hypertension the smaller differences between the Cape Coloured and whites become even less evident.

Patients suffering from nephrosis and diabetes are unusually prone to atherosclerosis. Nephrosis was too infrequently encountered in our autopsy series to have influenced the results and, as we have pointed out above, diabetes was probably not an important factor in determining racial differences. A decreased incidence of aortic atherosclerosis has been observed in cirrhosis of the liver[14] but the incidence of cirrhosis in our autopsy material is only slightly higher in the Bantu than in the whites and is lowest in the Cape Coloured.[15] A lower incidence of severe atherosclerosis in malignant disease has been reported[16] but there was no significant difference in the over-all incidence of malignant disease in the 3 racial groups in our series.

Although the Bantu does on occasions get severe coronary atheroma, the rarity of myocardial infarction has been confirmed by our study and by a review of the protocols of a larger autopsy series. But in myocardial infarction, with or without thrombosis, the degree of luminal narrowing is more significant than the amount of atheroma in the coronary arteries. It should therefore be stressed that in this series not one of the cases classified as severe coronary atherosclerosis in the Bantu showed the severe luminal narrowing so common in the whites. (Since completing this study we have encountered 1 case of severe luminal narrowing of the coronary arteries in a Bantu man aged 35, who had chronic nephritis with secondary hypertension and died of cerebral hemorrhage.) Myocardial infarction was less common in the Cape Coloured than in

the whites, even in groups in which severe coronary atherosclerosis was as common, or more common, in the Cape Coloured. It is possible that this apparent discrepancy is also the result of a lower proportion of the cases of severe coronary atheroma showing severe luminal narrowing in the Cape Coloured.

Summary

An autopsy survey of aortic and coronary atherosclerosis in patients dying in a general hospital in Cape Town has shown marked differences between the whites and the Bantu. These differences were clearly demonstrated by a direct comparison of Bantu and White men between the ages of 40 and 59. They probably also existed among older subjects and women although relatively few Bantu over the age of 60, and fewer women than men were unfortunately available for study.

Severe aortic and coronary atherosclerosis did on occasions occur in the Bantu but were much less common than in the whites. Severe luminal narrowing of the coronary arteries was particularly rare in the Bantu, and this is in keeping with the rarity with which they develop myocardial infarction. The aorta and coronary arteries of the Bantu often showed complete freedom from atherosclerosis in age groups in which it was rare to find such freedom in the whites.

The differences between the whites and Cape Coloured were much less pronounced than those between the whites and Bantu, were rather more apparent in men than women, and tended to disappear in the presence of aggravating factors such as hypertension. Even in groups in which severe coronary atherosclerosis was as commonly encountered in the Cape Coloured as in the whites, the Cape Coloured appeared to show a lower frequency of severe luminal narrowing. Attention has been drawn to the possibility that the differences between the total white and Cape Coloured populatios of Cape Town are greater than those revealed by this study, as only the lesser economically privileged of the whites were eligible for admission to the hospital that provided the material for the study.

Acknowledgment

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Summario in Interlingua

Un revista necroptic de atherosclerosis aortic e coronari in patientes morte a un hospital general de Capetown ha revelate marcate differentias inter le blancos e le bantus. Iste differentias esseva nettemente demonstrate per un comparation directe de masculos bantu e blanc inter le etates de 40 e 59 annos. Il es probabile que le mesme differentias existe etiam in masculos de etates plus avantiate si ben como in le feminas, sed infelicemente pauc bantus de etate de plus que 60 annos e minus feminas que homine esseva disponibile pro le studio.

Il es ver, sever atherosclerosis aortic e coronari esseva incontrate occasionalmente in bantus, sed tal casos esseva multo minus commun que inter le blancos. Sever restriction del passage del arterias coronar esseva particularmente rar in le bantus, un constatation que es ben de accordo con le facto que le disveloppamento de infarcimento myocardial es multo incommun in ille racia. Le aorta e le arterias del bantus esseva frequentemente sin le minime tracia de atherosclerosis a etates al qual le blancos sin signos de atherosclerosis es rar.

Le differentias inter le blancos e le mesticios de Capetown esseva multo minus pronunciate que inter le blancos e le bantus. Illos esseva plus apparente in masculos que in femininas e tendeva a disparer in le presentia de factores aggravatori, como per exemplo hypertension. In le gruppos in que sever atherosclerosis esseva tanto commun in mesticios como in blancos, le mesticios nonobstante pareva haber un minus alte frequentia de sever restriction del passage. Es signalate le possibilitate que le differentias inter le blancos e le mesticios de Capetown in lor totalitate es plus marcate que illos revelate per le presente studio, proque solmente le economicamente minus privilegiate blancos esseva eligibile pro le admission al hospital que provideva le material del presente studio.

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Inter-American Cardiology Congress

The Sixth Inter-American Congress of Cardiology, to be held in Rio de Janeiro, Brazil, August 14-20, will include symposia and round tables on Chagas' disease, surgery, congenital heart disease, rheumatism, electrocardiography, microbiophysiology and vectorcardiography.

Further information and registration forms may be obtained from Dr. Hugo Alqueres, Secretary, Av. Nilo Pecanha, 38, Rio de Janeiro, Brazil.

Obstruction of Left Ventricular Outlet in Association with Ventricular Septal Defect

By RONALD M. LAUER, M.D., JAMES W. DUSHANE, M.D., AND JESSE E. EDWARDS, M.D.

A VENTRICULAR septal defect either as an isolated malformation or as part of many developmental complexes is the most common single developmental lesion of the heart. In an overwhelming percentage of cases, hearts bearing a ventricular septal defect whether or not other conditions are associated have no additional intracardiac lesion that causes obstruction to the normal egress of blood from the left ventricle.

In a pathologic collection of 722 hearts bearing malformations, we have observed 10 cases in which a ventricular septal defect was associated with obstruction of the left ventricular outlet. The purpose of this communication is to describe the varied anatomic arrangements encountered in these 10 cases and to report on their clinical features as well as the objective functional studies, when done.

One additional case that was observed clinically and at operation is also reported. This is done since it serves to make more nearly complete the classification of those anatomic arrangements in which the common denominators are ventricular septal defect and obstruction to left ventricular outlet.

The hemodynamic derangements that obstruction of the left ventricular outlet adds to a ventricular septal defect depend on the anatomic interrelationship between the ventricular septal defect and the site of obstruction and on the size of the defect itself. When the defect is large, the factor that determines the pressures in the chambers of the heart and the systemic circulation is the position of obstruction with respect to the interventricular communication. When the defect is small, it does not of itself affect the hemodynamics significantly.

In an introductory manner, it is to be emphasized that in some of the anatomic patterns the site of left ventricular obstruction lies proximal to the ventricular septal defect, while in others this relationship is reversed. In the former situation, the right ventricle and aorta lie in the same compartment, which is separated from the left ventricle by the site of left ventricular stenosis. Here, on anatomic grounds, it would be anticipated that the right ventricle and aorta would exhibit essentially similar systolic pressures, while the systolic pressure in the left ventricle would be of a higher order.

In the situation wherein the site of left ventricular obstruction lies distal to the ventricular septal defect, the 2 ventricles share a systolic compartment. The zone of obstruction lies between this systolic compartment and the aorta. Here, on anatomic grounds, it would be anticipated that the 2 ventricles would exhibit essentially equal systolic pressures, while the aortic pressure would be of a lower order.

These cases are presented in the framework of a classification based upon size of defect and site of obstruction. Some of the hemodynamic considerations are derived from direct measurements of pressure and saturation. In other instances, in which only limited or no direct measurements were made, certain assumptions based upon established physiologic principles are justified from the anatomic arrangements.

The varied arrangements of obstruction to left ventricular outlet coexisting with a ven

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Table 1

Classification of Obstruction to Left Ventricular Outlet in Association with Ventricular Septal Defect

I. Right ventricle freely in communication with aorta or left ventricle
  1. Right ventricle and aorta in free communication
    a. Subaortic stenosis below a large ventricular septal defect
    b. Origin of both great vessels from the right ventricle with a very small ventricular septal defect as the only route of egress from the left ventricle
  2. Right ventricle and left ventricle in free communication
    a. Subaortic stenosis above a large ventricular septal defect
    b. Anomalous chordal insertion of the anterior mitral leaflet causing obstruction of left ventricular outflow above a large ventricular septal defect
    c. Subaortic stenosis opposite a large ventricular septal defect

II. Right ventricle *not* in free communication with left ventricle or aorta
  Coexisting right ventricular infundibular stenosis and subaortic stenosis associated with a small ventricular septal defect

tricular septal defect which we have encountered are illustrated in figures 1, 2, and 3. Some of these cases have been reported previously.[1, 2] They are again mentioned in this communication in the context of a classification (table 1).

I. Right Ventricle Freely in Communication with the Aorta or Left Ventricle

1. Right Ventricle and Aorta in Free Communication

a. Subaortic Stenosis Below a Large Ventricular Septal Defect (Case 1)

Clinical Features. A diabetic boy who was first seen at the Mayo Clinic in 1951 at the age of 4½ years had been known to have a cardiac murmur from infancy. Examination in 1951 revealed a continuous murmur in the left infraclavicular fossa and a loud systolic murmur and thrill at the lower left sternal border. The thoracic roentgenogram revealed cardiomegaly with normal pulmonary arterial and aortic segments, and the pulmonary vasculature was normal. The electrocardiogram was interpreted as showing right ventricular hypertrophy. The working clinical diagnosis was patent ductus arteriosus. However, because some of the findings were unusual for classic patent ductus arteriosus, cardiac catheterization was advised. It was refused by the parents.

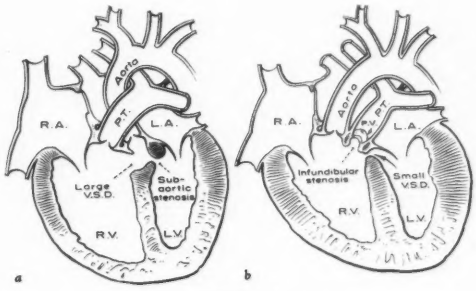

Figure 1

Ventricular septal defect in association with obstruction to the left ventricular outlet. Right ventricle and aorta in free communication. a. *Subaortic stenosis below a large ventricular septal defect (case 1).* b. *Origin of both great vessels from the right ventricle with a small ventricular septal defect as the only route of egress from the left ventricle (case 3). Pulmonary valvular and right ventricular infundibular stenosis were also present.*

Exploratory thoracotomy was recommended in the hope that the lesion was a patent ductus arteriosus, correction of which would lead to definitive cure. At operation on May 3, 1952, the ductus arteriosus was found to be closed. No further exploration was done.

After an uneventful postoperative recovery the patient was followed over the next 8 years; his diabetes and cardiac lesion caused him little difficulty. In 1958, at 12 years of age and following a respiratory illness, the patient had signs of congestive heart failure and returned for care. He was admitted to the hospital on February 18, 1958, and treated with digoxin and diuretics; the congestive failure was relieved rapidly. Examination at that time revealed a thrill and a grade IV systolic murmur (graded on a basis of I to IV) at the lower left sternal border. The murmur was widely transmitted; it had a more musical quality at the apex, and extended to the axilla. At the base there was a grade-I diastolic murmur which with the systolic murmur gave a continuous bruit. The second sound in the pulmonary area was single and not accentuated. The thoracic roentgenogram (fig. 4*a*) showed moderate cardiomegaly and normal pulmonary vascular markings. The electrocardiogram (fig. 4*b*) showed sinus rhythm, a rate of 100 per minute, a P-R interval of 0.2 second, incomplete right bundle-branch block with a QRS complex lasting 0.11 second and an axis of +120°, and was interpreted as showing right ventricular hypertrophy, digitalis effect, and no evidence of left ventricular hypertrophy.

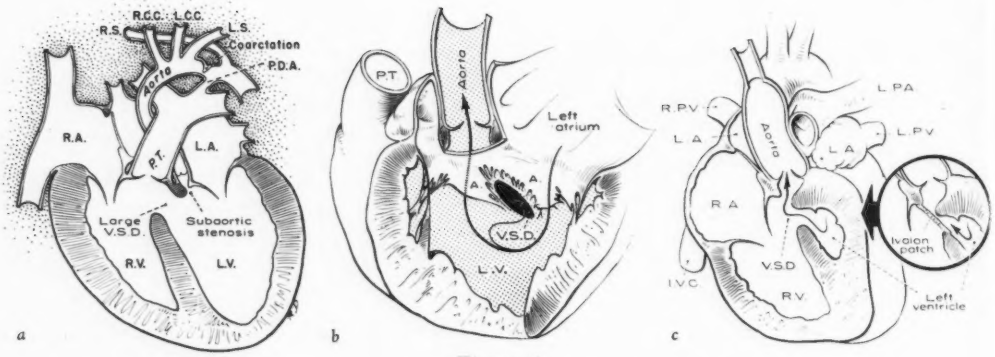

Figure 2

Ventricular septal defect in association with obstruction to the left ventricular outlet. Right and left ventricles in free communication. a. *Subaortic stenosis above a ventricular septal defect (cases 4 to 8). In this complex, reported by Becu and associates,[2] intracardiac defects are associated with obstruction of the aortic arch and a patent ductus arteriosus communicating with the descending aorta. (Reproduced with permission from: Becu, L. M., Tauxe, W. N., DuShane, J. W., and Edwards, J. E.: A complex of congenital cardiac anomalies: Ventricular septal defect, biventricular origin of the pulmonary trunk, and subaortic stenosis. Am. Heart J.* **50**: *901, 1955.)* b. *Anomalous chordal insertion of the anterior mitral leaflet causing obstruction of the left ventricular outlet in association with a ventricular septal defect of the type in the complex known as persistent common atrioventricular canal (case 9). In this case the peculiar chordal insertion of the cleft anterior mitral leaflet caused obstruction in the left ventricular outlet. The letter "A" appears on each half of the cleft anterior mitral leaflet.* c. *Subaortic stenosis opposite a ventricular septal defect (case 10). No functional obstruction to the left ventricular outlet exists when the ventricular septal defect is present. As shown in the insert, when the defect was closed with a prosthetic patch (Ivalon) the existing mass of muscle in the left ventricular outlet was effective in causing left ventricular obstruction.*

Cardiac catheterization was done on March 28, 1958 (table 2), and the patient was dismissed from the hospital without evidence of congestive heart failure. He was to return for evaluation in several weeks. About 3 weeks later he became suddenly ill with fever and prostration. He was admitted to the hospital in his home community but died shortly thereafter (on April 13, 1958) in congestive heart failure.

Pathologic Features. Necropsy performed by one of us (J.E.E.) disclosed in the upper part of the outflow tract of the left ventricle a severe degree of subaortic stenosis (fig. 5*a*) in which the lumen of the tract was reduced to a diameter of only 7 mm. The zone of obstruction was characterized by a cylindrical deposit of dense fibrous tissue involving the anterior wall of the left ventricle, the ventricular septum, and the ventricular aspect of the anterior leaflet of the mitral valve. The zone of obstruction extended for about 8 mm. in a supero-inferior direction. Its uppermost aspect lay about 1 cm. below the lower part of the aortic valve.

Immediately above the site of subaortic stenosis was a ventricular septal defect measuring 1.2 cm. in diameter (fig. 5*b*). On the left the defect lay beneath the posterior and right aortic cusps. On the right it lay immediately postero-inferior to the crista supraventricularis (fig. 5*c*).

In the left ventricle just above the upper edge of the ventricular septal defect and just below the aortic valve a membrane of fibrous tissue protruded horizontally into the lumen. At the level of this horizontal membrane the caliber of the left ventricular outflow tract was reduced to 1.0 cm.

The aortic valve orifice measured 2.2 cm. in diameter. The aortic cusps were irregularly thickened and moderately friable. Representative histologic examination of the aortic valve showed a picture of healing bacterial endocarditis.

The left ventricular wall was markedly hypertrophied, measuring 1.5 cm. in thickness. The right ventricle, though less thickened than the left was hypertrophied and 0.9 cm. thick.

The valves other than the aortic were normal

The foramen ovale and ductus arteriosus were closed. The coronary arteries were normal.

Histologic examination of the lungs showed edema, hemosiderosis, and medial hypertrophy of the arterioles and muscular arteries. No intimal lesions were identified in these vessels.

Comment. At catheterization of the right side of the heart a large left-to-right shunt at ventricular level was noted. There was close approximation of the systolic pressures in the right ventricle, pulmonary artery, and aorta—the findings usually associated with an uncomplicated large ventricular septal defect.

An area of subaortic stenosis was situated below the ventricular defect. Thus it may be assumed that the pressure in the left ventricle was elevated over that in the systolic compartment composed of the right ventricle, pulmonary artery, and aorta. This assumption of elevated left ventricular pressure is supported by the finding of undue left ventricular hypertrophy in the specimen.

In the face of clinical findings and the data obtained when the right side of the heart was catheterized, which were consistent with a large ventricular septal defect, it would be unusual to proceed with catheterization of the left side of the heart. However, if this had been done the presence of the subaortic stenosis probably would have been detected.

b. Origin of Both Great Vessels from the Right Ventricle with a Small Ventricular Septal Defect as the Only Route of Egress from the Left Ventricle (Case 2)

Clinical Features. The patient was first seen at the Mayo Clinic in 1948 at the age of 2½ years. A heart murmur had been noted at birth. Symptomatically, the patient had previously had 2 transient episodes of cyanosis, and became short of breath and perspired profusely with slight exertion. Physical examination revealed a thrill and a loud systolic murmur at the lower left sternal border. The second pulmonic sound was single. Ear oximetry showed a systemic arterial saturation of 85 per cent at rest and 77 per cent with exercise.

The radiologic configuration of the heart and electrocardiographic changes were consistent with the diagnosis of tetralogy of Fallot. However, the murmur was not considered typical of this condition.

Three years later, in 1951, at another center, the heart was catheterized. The findings (table 3) were consistent with a diagnosis of tetralogy of Fallot. Therefore a Brock valvotomy ("closed" pulmonary valvotomy and infundibular resection) was done in 1951.

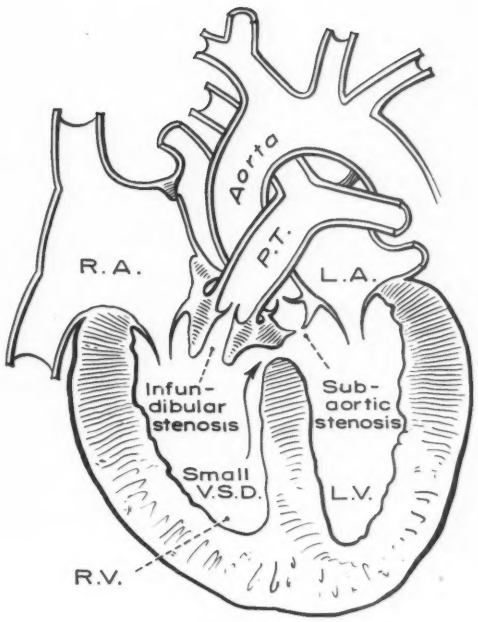

Figure 3

Ventricular septal defect in association with obstruction to the left ventricular outlet. Right ventricle not *in free communication with the left ventricle or aorta. Coexisting right ventricular infundibular stenosis and subaortic stenosis with a small ventricular septal defect (case 11).*

The patient was next seen at the Mayo Clinic in 1958 at the age of 13 years. He had no visible cyanosis and only slight limitation of exercise. Physical examination revealed a thrill at the lower left sternal border and a very loud, grade-IV systolic murmur heard in the same area and extending to the base, axilla, apex, and posterior part of the thorax. Diastole was clear. The second sound in the pulmonic area was single and of normal intensity. A thoracic roentgenogram showed moderate cardiomegaly, an upturned apex, a concave pulmonary segment, and normal pulmonary vascular markings (fig. 6*a*). The electrocardiogram showed sinus rhythm, a rate of 75 per minute, and an axis of −130°; it was interpreted as showing right ventricular hypertrophy and no evidence of left ventricular hypertrophy (fig. 6*b*).

Table 2

Synopsis of Cardiac Catheterization Data in Case 1 (Subaortic Stenosis Below a Large Ventricular Septal Defect)*

Site of sampling	Pressure, mm. Hg	Oxygen saturation, per cent†
Superior vena cava	—	63
Right atrium	21/8	58
Right ventricle	107/11-24	79-88
Pulmonary artery	117/49	89-91
Femoral artery	117/59	100

*Pressure and saturation data obtained during administration of 100 per cent oxygen.

†Saturations determined with cuvette oximeter. Dye-dilution curves from the right side of the heart with sampling at the radial artery revealed a right-to-left shunt of about 5 per cent. The left-to-right shunt calculated from saturation data was about 54 per cent.

The patient was referred for corrective cardiac surgical treatment, with a diagnosis of ventricular septal defect associated with pulmonic stenosis and pulmonary blood flow greater than usually exists with this combination.

At operation, under conditions of extracorporeal circulation, both great vessels were found to arise from the right ventricle. The only route of egress of blood from the left ventricle was through a tiny ventricular septal defect measuring about 6 by 4 mm. There was subpulmonary infundibular and pulmonary valvular stenosis. The ventricular septal defect was enlarged. A Teflon channel was sutured between the surgically enlarged ventricular septal defect and the root of the aorta. The pulmonary tract was widened by valvotomy of a stenotic bicuspid pulmonary valve and placement of a Teflon-Ivalon prosthesis in the anterior wall of the right ventricle and origin of the pulmonary trunk. The patient died shortly after operation.

Pathologic Features. As seen from the exterior of the heart the pulmonary trunk and the aorta had normal relationships. From the interior view of the heart, however, the aortic valve was seen to lie to the right of the pulmonary valve and at a plane that was only slightly inferior to that of the pulmonary valve (fig. 7*a*). The operative findings, namely origin of both great vessels from the right ventricle, and a small ventricular septal defect, were confirmed. There was considerable hypertrophy of both ventricles, the left being 1.9 cm. thick (fig. 7*b*) and the right 1.0 cm. thick. Evidence for elevated left ventricular pressure related to obstruction at the small ventricular septal defect was additionally supported by a prominent jet lesion on the anterolateral aspect of the right ventricle opposite the ventricular septal defect and just beneath the aortic valve. The atrial septum showed a very small defect based upon a short valve of the foramen ovale.

Table 3

*Synopsis of Cardiac Catheterization Data in Case 2**

Chamber	Pressure, mm. Hg	Oxygen saturation, per cent†
Superior vena cava		60
Right atrium	0 to –4	63
Right ventricle at apex		74
Right ventricle at pulmonary valve	62/0	73
Right pulmonary artery	8/0	74
Pulmonary veins	4/–2	99
Aorta via right ventricle	62/54	84

*Cardiac catheterization done at the University of Minnesota Hospitals in Minneapolis in 1951 and presented here with their permission.

†Cuvette method.

Histologic examination revealed normal to thinner-than-normal arterioles in the lungs and widened arterioles in the visceral pleura, suggesting an enlarged collateral system to the lungs.

Comment. In this condition the right ventricle and aorta are in the same hemodynamic vascular compartment, which may be termed "right ventricular-aortic compartment." The presence or absence of pulmonic stenosis determines whether the pulmonary artery is in free communication with this compartment.

A case similar in some respects to this was reported by Edwards and associates[1] in 1952. For completeness in reporting our material it is included here as case 3. These authors described a heart in which both great vessels arose from the right ventricle and were associated with a small membranous ventricular septal defect that was sealed by the adhesion of the anterior mitral leaflet to its edges. There was a tiny accessory opening in the anterior mitral leaflet that corresponded in position with the adhesion of the mitral valve to the septal defect, thus allowing communication between the left atrium and the right ventricle. This opening and a small patency

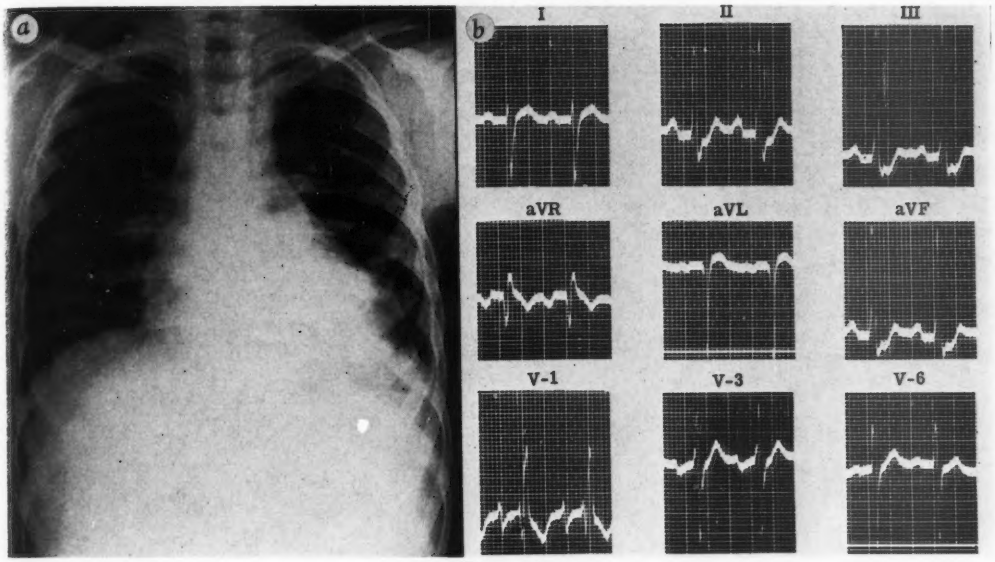

Figure 4

Subaortic stenosis below a large ventricular septal defect (case 1). a. *Posteroanterior roentgenogram of thorax.* b. *Electrocardiogram.*

at the foramen ovale were the only routes of egress from the left side of the heart. There was no infundibular or valvular pulmonary stenosis. Thus the right ventricle, aorta, and pulmonary artery were in the same systolic compartment. The left ventricle was separated completely from this compartment. It is reasonable to assume, therefore, that equal systemic systolic pressures had existed in the right ventricle, pulmonary artery, and aorta, while the left atrial pressure and left ventricular pressure were markedly elevated above normal.

In the case reported herein (case 2) the left ventricle and pulmonary artery were separated from the right ventricular-aortic compartment by a very small ventricular septal defect and by infundibular and valvular pulmonary stenosis respectively. These anatomic considerations make understandable the facts demonstrated by cardiac catheterization that the right ventricular and aortic systolic pressures were equal and that a pressure gradient existed across the pulmonary valve. It is assumed that in the left ventricle, since its only outlet was a small ventricular septal defect, the systolic pressure was greater than in either the right ventricle or the aorta. The hypertrophy of the left ventricle and the jet lesions in the right ventricle opposite the ventricular septal defect support this view.

The anatomic arrangements are such that catheterization of the right side of the heart yields findings similar to those in tetralogy of Fallot.

It is of interest to postulate that differentiation of this situation might have been accomplished by special technics (catheter position or angiocardiography) that would have demonstrated that the aortic valve lay more to the right and at a more superior plane than it does in tetralogy of Fallot. Further, selective angiography of the left atrium or left ventricle might have allowed the left ventricular obstruction to have been suspected, especially if it were combined with angiography of the right side of the heart. The former might have revealed the small ventricular septal defect with perhaps delayed emptying of the left ventricle. The latter might have demonstrated the abnormal origin of the aorta.

2. Right Ventricle and Left Ventricle in Free Communication

a. Subaortic Stenosis Above a Ventricular Septal Defect (Cases 4 to 8)

A group of five cases was reported from the Mayo Clinic in 1955 by Becu and associates.[2] These portrayed an anatomic complex of a ventricular septal defect situated anteriorly in the right ventricular outflow tract (not involving the membranous septum), subaortic stenosis resulting from a muscular ridge lying across the outflow tract of the left ventricle, obstructive anomalies of the aortic arch system (interruption of the aortic arch or coarctation), and patent ductus arteriosus. A similar case was noted by Taussig.[3] A diagrammatic representation is shown in figure 2*a*.

Comment. In the 5 cases reported by Becu and associates[2] each infant died during its first month of life. None had cardiac catheterization.

In this situation both ventricles and the pulmonary artery are in the same systolic compartment. Subaortic stenosis separates the ascending aorta from this compartment; coarctation or interruption of the arch separates the ascending aorta from the descending aorta. A patent ductus arteriosus connects the pulmonary artery with the descending aorta. Thus it can be assumed that equal systolic

Figure 5

Subaortic stenosis below a large ventricular septal defect (case 1). a. *The left ventricle viewed from below. In the outflow tract (point of arrow) is a constricting fibrous ring representing the lower portion of the subaortic stenosis. L.V. = left ventricle. L.A. = left atrium. The anterior leaflet of the mitral valve is photographed from the perspective of its lower edge.* b. *The subaortic portion of the left ventricle and the aortic valve opened. The subaortic stenosis lies above the point of the arrow. The ventricular septal defect (D.) lies above the subaortic stenosis. Vegetations of bacterial endocarditis are present upon the aortic valve. Between the aortic valve and the ventricular septal defect a semicircular shelf of fibrous tissue protrudes into the subaortic tract. A.M. = anterior leaflet of mitral valve.* c. *Right ventricle and pulmonary valve. The ventricular septal defect (D.) lies below the crista supraventricularis and above the papillary muscle of the conus (P.M.C.). P.V. = pulmonary valve. R.V. = inflow portion of right ventricle.*

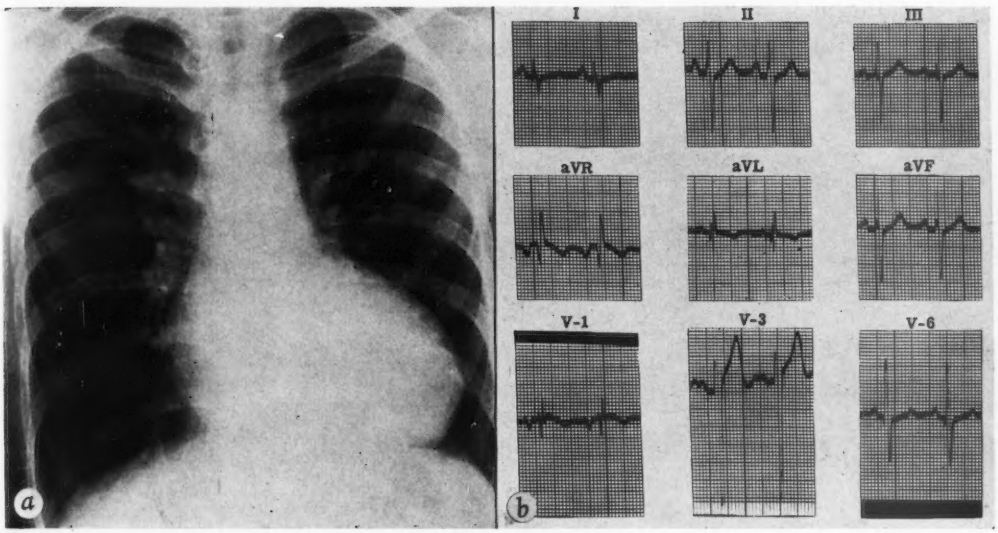

Figure 6

Origin of both great vessels from the right ventricle with a small ventricular septal defect as the only route of egress from the left ventricle (case 2). a. *Posteroanterior roentgenogram of thorax.* b. *Electrocardiogram.*

pressures existed in the right ventricle, left ventricle, pulmonary artery, and descending aorta, while the pressure in the ascending aorta was lower than in these chambers or vascular segments.

b. Anomalous Chordal Insertion of a Cleft Anterior Mitral Leaflet Causing Obstruction of Left Ventricular Outflow in Association with a Ventricular Septal Defect of the Persistent Common Atrioventricular Canal Type (Case 9)

Clinical History. A 26-month-old girl was referred to the Mayo Clinic for cardiac evaluation in 1958. She had a heart murmur known from 7 weeks of age. During the first 15 months of life she had gained poorly and had had frequent episodes described as pneumonia. Since the age of about 16 months her general condition had improved. She had gained weight more rapidly and the respiratory infections recurred less often. There was no history of exertional dyspnea, cyanosis or anoxic episodes.

Physical examination showed a very small but vigorous female child. Her heart was moderately hyperactive. There was no thrill. There was a grade II systolic murmur maximal at the second left interspace with extension to midprecordium and fading toward the apex. There was a grade II diastolic murmur maximal at the second and third left interspaces. The second pulmonic sound was moderately accentuated and split. The blood pressure in the brachial artery determined by the cuff method was 120 mm. Hg systolic and 80 mm. diastolic. The femoral pulsations were easily palpable bilaterally.

A thoracic roentgenogram (fig. 8*a*) showed moderate cardiomegaly with a full pulmonary arterial segment and increased pulmonary vascular markings. The electrocardiogram (fig. 8*b*) showed sinus rhythm, a rate of 120 per minute, and an axis of −70°. The changes were interpreted as those of right ventricular hypertrophy, with evidence of left ventricular overload for age. The latter was thought to be present because of the counterclockwise frontal loop in the frontal plane with marked left axis deviation of the mean QRS vector in so young a patient. Although the electrocardiogram in itself was suggestive of persistent common atrioventricular canal, the total clinical picture was considered more consistent with that of the usual ventricular septal defect with associated pulmonary valvular insufficiency. The patient was referred for surgical repair with the aid of extracorporeal circulation.

At operation, before the heart was opened, the pressure in millimeters of mercury was 108/54 in the pulmonary artery and 106/10 in the right ventricle, while the cuff pressure in the brachial artery was 105/80. A small patent ductus arteriosus was

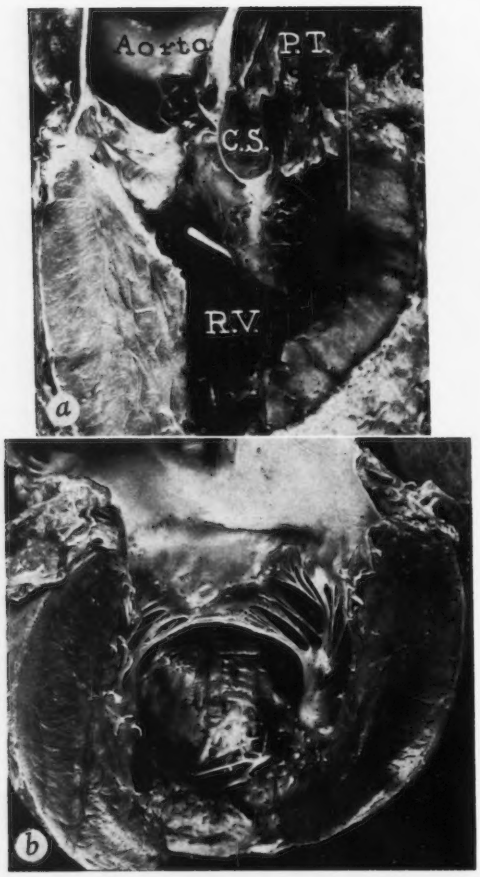

Figure 7

Origin of both great vessels from the right ventricle with a small ventricular septal defect as the only route of egress from the left ventricle (case 2). a. *Outflow portion of right ventricle (R.V.). The aorta rises exclusively from the right ventricle beside the pulmonary trunk (P.T.). The subpulmonary portion of the outflow tract is somewhat narrowed, in part by the presence of the hypertrophied crista supraventricularis (C.S.). The position of the narrow ventricular septal defect is marked by the presence of a probe. Opposite the ventricular septal defect and immediately beneath the aortic valve there is endocardial thickening of the right ventricle representing a reaction to the impact of the jetlike stream coming from the small ventricular septal defect.* b. *Left atrium and left ventricle. Marked left ventricular hypertrophy. There is anatomic evidence of the obstructive nature of the small ventricular septal defect (defect not shown in this perspective).*

ligated. Palpation over the left atrium revealed no thrill of mitral insufficiency. On opening the right atrium, no atrial septal defect or tricuspid insufficiency was noted.

Through an incision in the right ventricle, a ventricular septal defect in the position of the common atrioventricular canal was noted. This defect lay under a slightly cleft septal tricuspid leaflet. The defect was repaired with a Teflon prosthesis.

When the heart had resumed action following the repair, the systolic pressure was 90 to 95 mm. Hg in the pulmonary artery and right ventricle, and 95 to 100 in the aorta and left ventricle. Thus no fall in pulmonary pressure followed repair. After extracorporeal circulation, the patient's condition was precarious and about 1 hour postoperatively she died.

Pathologic Features. A ventricular septal defect was present beneath the anterior leaflet of the mitral valve and the septal leaflet of the tricuspid valve. On the right side the defect extended to the crista supraventricularis. While the anterior extent of the defect was not unusual, the fact that it extended farther under the septal leaflet of the tricuspid valve than usual placed it in the category of an interventricular communication in persistent common atrioventricular canal (fig. 9*a*). The septal leaflet of the tricuspid valve had a small cleft. Viewed from the left side (fig. 9*b*) the defect lay beneath the anterior leaflet of the mitral valve. The mitral valve was the site of gross abnormality with a cleft involving the anterior leaflet. The chordal attachments of the mitral valve were abnormal. There were 2 sets of papillary muscles and the usual posteromedial and anterolateral sets of chordae. In addition to these chordae there were chordae that ran from the edges of the cleft of the anterior leaflet of the mitral valve and inserted into the ventricular septum. This made the anterior half of the anterior mitral leaflet relatively immobile and caused the approach to the outflow tract of the left ventricle to be relatively confined. The confined area lay between the ventricular septum, the anterolateral commissure of the mitral valve, the anterior half of the anterior mitral cusp, and the chordae that joined the anterior half of the anterior mitral cusp to the ventricular septum. The lower part of the outflow tract was thereby compromised, measuring only about 1 cm. in diameter.

The aortic arch system was anomalous. Five branches arose from it. The first branch was the right common carotid artery, the second the left common carotid artery, the third the left vertebral, and the fourth the left subclavian; each of these arose from the most superior aspect of the aortic

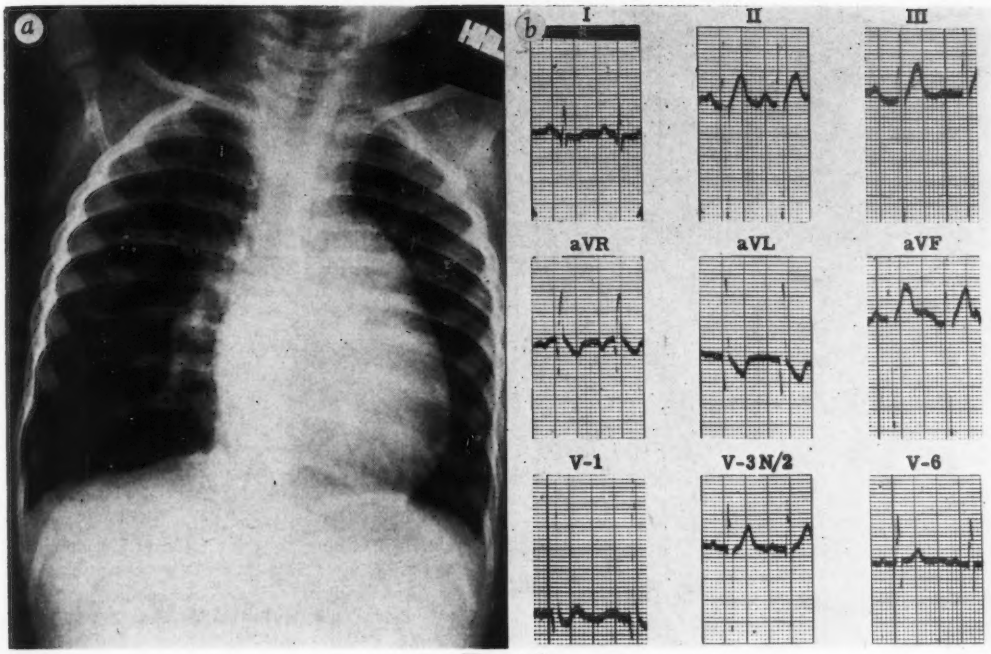

Figure 8

Anomalous chordal insertion of the anterior mitral leaflet causing obstruction of left ventricular outflow in association with a large ventricular septal defect (case 9). a. *Posteroanterior roentgenogram of thorax.* b. *Electrocardiogram.*

arch. Arising as the fifth branch of the arch, and from the posterior wall of it, was the right subclavian artery, which passed behind the esophagus to reach the right arm.

Immediately distal to the origin of the right subclavian artery was a site of typical coarctation at which the aortic lumen measured 3 mm. in diameter. Distal to the coarctation was a slightly patent ductus arteriosus, which had a lumen of 3 mm. as it joined the aorta.

Histologic examination of the lungs revealed marked (grade IV) changes of hypertensive pulmonary vascular disease, characterized by the formation of plexiform lesions and generalized arterial dilatation.[4]

Comment. In this case the insertion of the anterior mitral leaflet resulted in obstruction to left ventricular outflow above the ventricular septal defect. This anatomic arrangement creates an intracardiac functional situation which resembles that in the cases reported by Becu and co-workers.[2] The right ventricle, pulmonary artery and left ventricle were in the same systolic compartment, while the left ventricular outflow tract and the ascending aorta were separated from the intracardiac systolic compartment by the anomalously inserted anterior mitral leaflet. The descending aorta was separated from the ascending aorta by a coarctation and from the pulmonary artery by a very small patent ductus arteriosus.

Thus it may be assumed that the systolic pressure was uniform in the right ventricle, pulmonary artery and left ventricle, decreased in the ascending aorta, and still further decreased in the descending aorta.

c. Subaortic Stenosis Opposite a Ventricular Septal Defect (Case 10)

In our collection is another case portraying subaortic stenosis opposite a ventricular defect but without obstruction of the aorta itself.

Clinical History. A 3½-year-old girl was referred to the Mayo Clinic in 1958. She was known to have had a murmur from 2 months of age. The parents had noticed that she had always be-

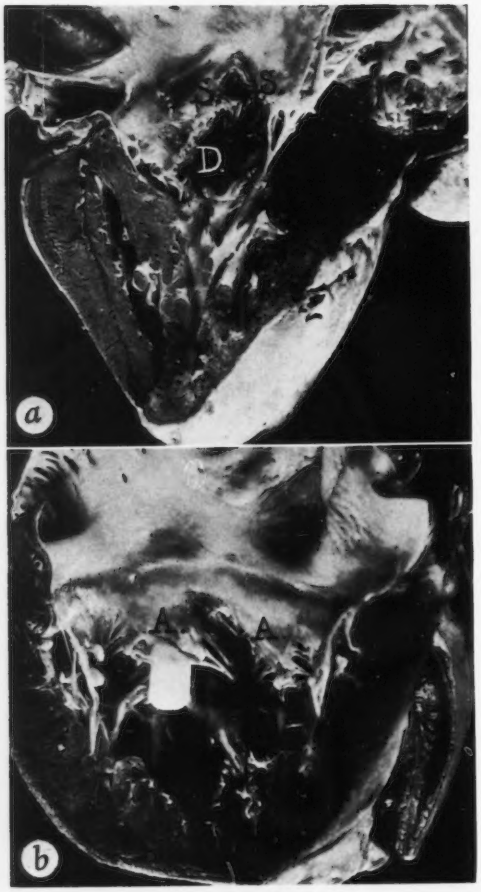

Figure 9

Anomalous chordal insertion of the anterior mitral leaflet causing obstruction of left ventricular outflow in association with a large ventricular septal defect (case 9). a. *Right atrium and ventricle. The septal leaflet of the tricuspid valve (S.) has a small cleft above the ventricular septal defect (D.) of the type seen in persistent common atrioventricular canal. There is hypertrophy of the right ventricle. The atrial septum is intact.* b. *Left atrium and left ventricle. A ventricular septal defect of the type seen in persistent common atrioventricular canal lies opposite and below a cleft in the anterior mitral leaflet (A.). The anterior mitral leaflet has both normal and abnormal chordal attachments. The normal attachments are to the papillary muscles. The abnormal attachments run from the edges of the cleft in the leaflet to the ventricular septum. The peculiar chordal attachments of the anterior half of the cleft anterior leaflet cause obstruction to the left ventricular outflow (containing probe). The obstruction is caused by the chordae holding the leaflet taut near the ventricular septum. There is left ventricular hypertrophy. The atrial septum is intact.*

come easily fatigued and manifested grunting respirations with slight exertion. Cyanosis had never been observed.

At 1 year of age, cardiac catheterization performed at another center had revealed a left-to-right shunt at the ventricular level, with pressures in millimeters of mercury as follows: right ventricle 70/0-11, pulmonary artery 65/25, left ventricle 86/0-12, and aorta 86/50. The catheter entered the aorta and left ventricle from the right ventricle. During the next 2 years the patient had gained fairly well but continued to fatigue easily.

At the age of 3½ years physical examination revealed an overactive heart, a grade-III systolic murmur maximal at the fourth left interspace with extension to the second left interspace and the apex. There was an apical diastolic inflow rumble. The second sound in the pulmonic area was split and the second component was moderately accentuated.

The thoracic roentgenogram (fig. 10*a*) revealed moderate cardiomegaly, an enlarged pulmonary artery segment, and markedly increased pulmonary vascular markings. The electrocardiogram (fig. 10*b*) showed sinus rhythm, a rate of 109 per minute, a P-R interval of 0.20 second, an axis of −110°, right ventricular hypertrophy, and left ventricular hypertrophy.

The clinical diagnosis was ventricular septal defect with pulmonary hypertension and a large left-to-right shunt. Operation was advised.

During thoracotomy but before any repair, the pressure was 79/6 in the right ventricle and 95/41 in a systemic artery.

With the aid of extracorporeal circulation and asystole, 2 ventricular septal defects were identified. One was in the usual location, lying posteroinferior to the crista supraventricularis and extending under the tricuspid ring along almost the entire extent of its septal leaflet. This defect measured 1.6 cm. in diameter. A second defect in the crista supraventricularis was represented by 2 small openings, one measuring 2 mm. and the other 4 mm. in diameter. Muscular tissue was present between this defect and the pulmonary valve. The large defect was closed by placement of an Ivalon sponge. The smaller (muscular) defects were closed by direct suture. After the right ventricle had been closed and the heart had resumed its function the pressure was 32/7 in the right ventricle and 88/36 in a systemic artery.

Immediately following the surgical procedure

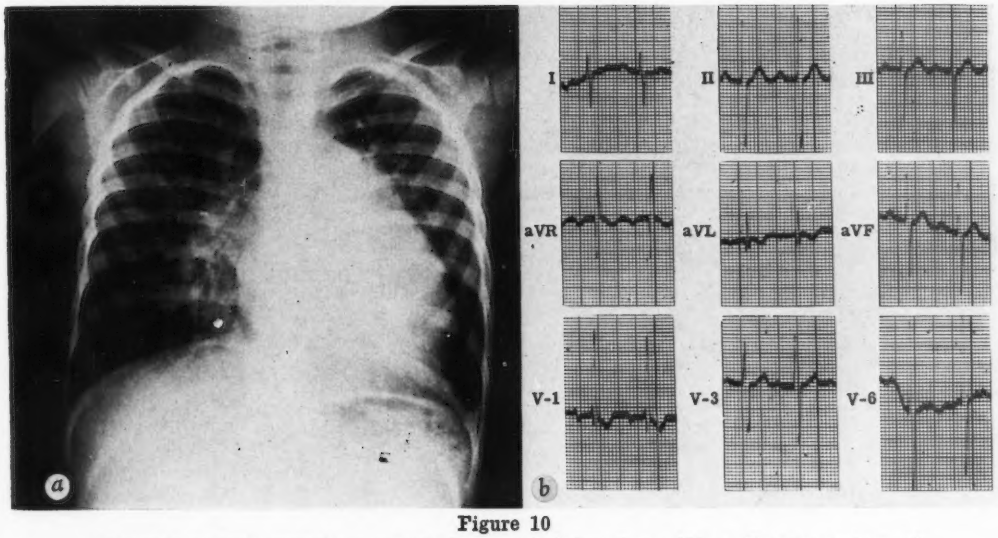

Figure 10

Subaortic stenosis opposite a ventricular septal defect (case 10). a. *Roentgenogram of thorax.* b. *Electrocardiogram.*

complete heart block was noted. All measures failed to maintain an adequate systemic blood pressure, and death occurred 24 hours postoperatively.

Pathologic Features. Necropsy revealed the repaired defects described. From the left ventricular aspect a mass of muscle was seen protruding from the upper part of the muscular ventricular septum and adjacent anterior left ventricular wall. The mass lay at the level of the larger ventricular septal defect, and so, slightly below the aortic valve. It protruded into the left ventricular outflow tract and narrowed it to a diameter of 1.0 cm. (fig. 11). The position of the protruding mass was such that repair of the ventricular septal defect with the prosthetic patch caused the outflow tract to become obstructed. Apparently, before the patch was placed, blood could be diverted around the mass in the space of the septal defect and so reach the aorta without barrier (fig. 2*c*).

The smaller defects of the ventricular septum that were observed and closed during the operation opened into the left ventricle through the proximal portion of the protruding mass described.

The left ventricle and right ventricle were hypertrophied, their walls being 1.2 and 0.8 cm. thick respectively. The left atrium was dilated and its endocardium was uniformly thickened. The valves were normal. The ductus arteriosus was closed.

Histologic sections of the lungs showed mild medial hypertrophy and no significant intimal lesions.

Comment. In this case there was subaortic stenosis opposite a ventricular septal defect. Unobstructed flow to the aorta from the left ventricle was considered to have been present before the larger defect was closed. Before closure, the hemodynamic aspects were similar to those frequently encountered in uncomplicated ventricular septal defects.

When the defect was closed the detour allowing free egress from the left ventricular chamber was abolished and obstruction to left ventricular outflow resulted. Although the pressure measured in the peripheral systemic circuit following repair of the defect was at first within normal range, it may be assumed from the anatomic details that postoperatively the left ventricular pressure was elevated above that measured in the aorta.

II. Right Ventricle Not in Free Communication with the Left Ventricle or Aorta

1. Coexisting Right Ventricular Infundibular Stenosis and Subaortic Stenosis Associated with Small Ventricular Septal Defect (Case 11)

In 1957 a 13-year-old girl was referred to the Mayo Clinic for cardiac evaluation and treatment. She was known to have had a heart murmur from birth. Her growth and development had been normal. During the previous year she had had easy fatigability, dyspnea with slight exertion, and periods of orthopnea. There was no history of cyanosis or anoxic episodes.

Figure 11

Subaortic stenosis opposite ventricular septal defect (case 10). a. *Left ventricle and aorta. In the postoperative state the Ivalon sponge used to close the large ventricular septal defect is in place. The 2 probes lie in the 2 channels representing the small ventricular septal defect. Above these a mass of muscle (Su.S.) protrudes from the ventricular septum and the anterior wall into the left ventricular cavity opposite the larger ventricular septal defect.* b. *The left ventricle in essentially the same perspective as shown in* a *but with the prosthesis used to close the larger ventricular septal defect removed. The mass of muscle seen in the subaortic position (Su.S.) lies opposite the ventricular septal defect.* c. *Right ventricular aspect of the larger ventricular septal defect after the prosthesis has been removed. The mass of muscle protruding from the anterior septal wall of the left ventricle (Su.S.) is shown in its position opposite the larger ventricular septal defect. Before closure of the larger ventricular septal defect blood could be diverted around the mass of muscle to reach the aorta. After closure of the defect with the prosthetic device this route was eliminated and subaortic stenosis followed as illustrated in figure 2c.*

Physical examination revealed a large 13-year-old girl with normal color. There was a systolic thrill in the suprasternal notch, a grade-II, harsh stenotic type of systolic murmur in the first right interspace with transmission to the neck, and a grade-III, harsh systolic murmur maximal in the third left interspace with extension to midprecordium and the apex. Neither the pulmonic nor the aortic second sound was audible. Diastole was clear. The femoral pulsations were normal. The blood pressure in the arms was 90/70.

The thoracic roentgenogram (fig. 12*a*) showed marked cardiomegaly. The pulmonary vascular markings were considered to be within normal range. The electrocardiogram (fig. 12*b*) showed sinus rhythm, a rate of 84 per minute, and right axis of +120°. There was evidence of combined overloading of both the right and the left ventricle.

A clinical diagnosis of combined pulmonary and aortic stenosis was made and surgical repair recommended.

At the time of thoracotomy but prior to any repair, the pressures in millimeters of mercury were: pulmonary artery 20/13, just below the pulmonary valve in the right ventricle 20/6, low in the right ventricle 170/6, left ventricle 188/9, and ascending aorta 108/61.

Under extracorporeal circulation, right ventriculotomy was performed. The right ventricular wall was markedly hypertrophied, being about 2.5 cm. thick. There was obvious infundibular stenosis, with an orifice 5 mm. in diameter, and a small infundibular chamber about 1 cm. in length beneath a normal pulmonary valve. There was a small ventricular septal defect about 5 mm. in diameter situated well behind the crista supraventricularis just at the angle between the anterior and septal leaflets of the tricuspid valve. The site

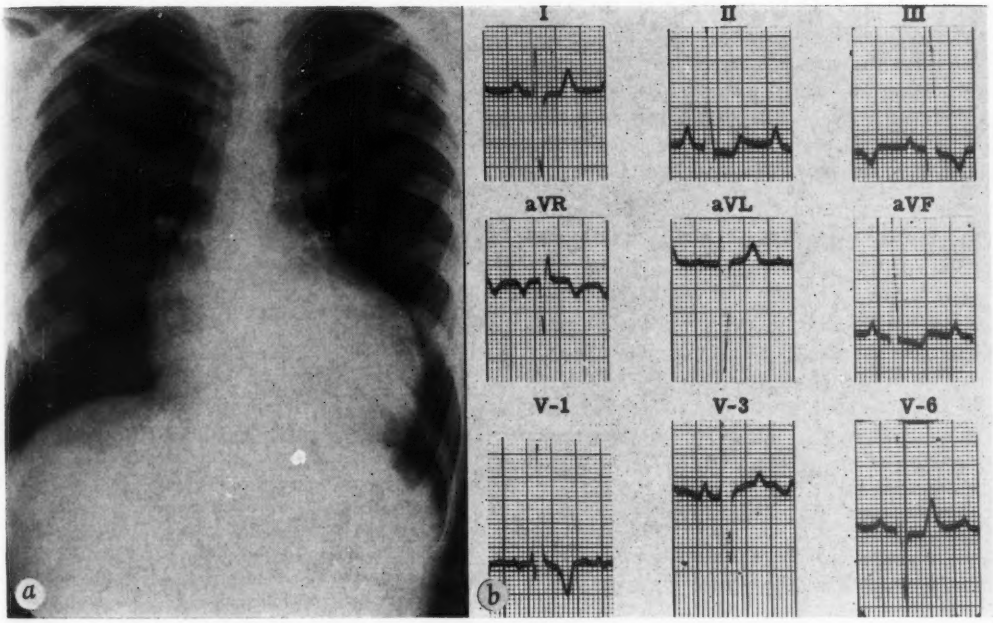

Figure 12

Subaortic stenosis and right ventricular infundibular stenosis with small ventricular septal defect (case 11). a. *Posteroanterior roentgenogram of thorax.* b. *Electrocardiogram. A diagrammatic representation of the malformations is shown in figure 3.*

of infundibular pulmonary stenosis was resected and the ventricular septal defect closed by direct suture.

On opening of the ascending aorta the aortic valve was found to be normal. Immediately beneath this valve was a tough but essentially membranous subaortic stenotic area with an orifice measuring about 6 mm. in diameter. Through the aortic valve an incision was made in the subaortic membrane.

When the heart had resumed normal action after repair of the defects the pressure in the left ventricle was 120/10, while the aortic pressure was 112/49. The pressure in the pulmonary artery was 35/14, while that low in the right ventricle was 41/6.

The patient had an uneventful postoperative recovery. When last seen 1 year postoperatively she had no symptoms referable to the cardiovascular system. She had a grade II to III systolic murmur in the second, third, and fourth left interspaces with extension to the neck, and a moderately loud, grade I to II diastolic murmur maximal in the third and fourth left interspaces. The clinical impression was that of aortic insufficiency, which may have been the result of gradual scarring of the aortic leaflets.

Comment. When a ventricular septal defect is tiny it contributes little to any hemodynamic situation.[5] In this case the elevated pressures in the ventricular chambers were the result of the stenotic outflow lesions. The pressure generated in each ventricular cavity depended only upon its relationship to the resistance offered by the stenotic lesion.

Although the pressures in the right and left ventricles prior to repair were almost of equal magnitude, this was considered to be fortuitous, for the ventricular septal defect was so small that free communication did not exist between the ventricular chambers.

Discussion

The cases presented herein are examples of ventricular septal defects associated with obstruction to the left ventricular outlet. The advent of surgical repair for ventricular septal defects has made the recognition of the complexes reported of practical significance. For, if the obstruction is unrecognized, repair of

the ventricular septal defect may leave the patient with obstruction to the left ventricular outlet or, in rare instances, may create obstruction that was not present preoperatively.

Clinically, isolated obstruction of left ventricular outflow is suspected when a murmur suggesting a stenotic lesion is heard in the aortic area, especially when the electrocardiogram shows evidence of left ventricular hypertrophy of the "systolic overload" type.[6]

In all but one (case 11) of the cases presented herein the murmurs were not recognized as those usually associated with obstruction to left ventricular outflow. In cases 1, 2, and 9 the lesions producing obstruction to left ventricular outflow were not related to the aortic valve, so that the murmurs produced were neither in the location nor of the quality of a usual aortic or subaortic stenosis.

In cases 4 to 8, wherein the subaortic stenosis was above the ventricular septal defect, the stenotic lesions were more closely related to the aortic valves. Perhaps in these cases phonocardiography, had it been done, would have revealed the "classic" diamond-shaped murmur of aortic stenosis.

In case 10 the obstruction was not present prior to operation. Thus, a murmur related to left ventricular obstruction could not be expected to exist preoperatively.

In cases 1, 2, and 11, left ventricular outflow was obstructed, and thus left ventricular overload patterns might be logically anticipated in the electrocardiogram. However, such patterns did not occur consistently. Only the case of coexisting right ventricular infundibular and subaortic stenosis associated with a very small ventricular septal defect (case 11) exhibited this electrocardiographic characteristic.

In cases 4 to 8 and 10 the obstruction to left ventricular outflow lay above the ventricular defect. The obstructing lesion in these anatomic arrangements did not result in left ventricular "systolic overload,"[6] for the obstruction could be bypassed through the ventricular septal defect and lead to a large left-to-right shunt.

In these cases electrocardiographic patterns were encountered that were like those in simple large ventricular septal defect with large left-to-right shunt. The observations are in concert with the hemodynamic features peculiar to these cases.

In cases 1 and 2, wherein the right ventricle was in free communication with the aorta, cardiac catheterization revealed equal right ventricular and systemic arterial systolic pressures, a relationship usually associated with an uncomplicated large ventricular septal defect or tetralogy of Fallot. With this anatomic arrangement, catheterization of the left side of the heart would be expected to demonstrate the obstructing lesion. However, since neither the auscultatory nor the electrocardiographic findings caused a suspicion of left ventricular obstruction, left ventricular pressures were not determined.

In cases 4 to 8, wherein the site of obstruction to the left ventricular outlet lay above a large ventricular septal defect and a large patent ductus arteriosus communicated with the descending aorta, one expects that there would be no differential in pressure between the 2 ventricles, the pulmonary artery and the descending aorta; but a differential would exist between the cardiac systolic compartment and the ascending aorta. Measurements of pressure in both the ascending and the descending aorta would be necessary to reveal the presence of the subaortic stenosis and the coarctation.

In the exceptional instance of case 10, obstruction is only potential, and preoperative studies of pressure would not indicate the presence of left ventricular obstruction.

Thus it can be seen that the preoperative diagnosis of left ventricular obstruction associated with a ventricular septal defect may prove not only difficult in some cases but impossible in others. While the auscultatory, roentgenographic, electrocardiographic, or cardiac-catheterization findings obtained by usual methods may readily establish the presence of a ventricular defect, they may not reveal that additional obstruction to the left ventricular outlet exists.

Summary

In a pathologic collection of 722 congenital heart lesions we have observed 10 cases in which a ventricular septal defect was associated with obstruction to normal left ventricular outflow. These cases are presented in the framework of a classification relating hemodynamics to the position of the obstructing lesion and the size of the ventricular septal defect. One additional case observed clinically and at operation is also reported to make more nearly complete the classification of the anatomic arrangements in which the common denominators are ventricular septal defect and obstruction to normal ventricular outflow.

Summario in Interlingua

In un collection pathologic de 722 congenite lesiones cardiac, nos ha observate 10 casos in que un defecto ventriculo-septal esseva associate con un obstruction del normal effluxo sinistro-ventricular. Iste casos es presentate intra un cadro de classification que relationa le hemodynamica al sito del lesion obstructive e al dimensiones del defecto ventriculo-septal. Es etiam reportate un caso additional que esseva observate clinica- e chirurgicamente pro render plus complete le classification del configurationes anatomic in que denominatores commun es defecto ventriculo-septal e obstruction al normal effluxo ventricular.

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Pericarditis is diagnosed in proportion to the care of the examination. —SIR WILLIAM OSLER. *Aphorisms From His Bedside Teachings and Writings.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 141.

Effect of Age on Pulse Wave Velocity and "Aortic Ejection Time" in Healthy Men and in Men with Coronary Artery Disease

By ERNST SIMONSON, M.D., AND K. NAKAGAWA, M.D.

THE INCREASE of pulse wave velocity with age is well established[1-3] and reflects a loss of the elastic properties of the arterial wall.[4] The age trends of pulse wave velocity vary for different arteries.[2, 5] In view of early localization of atherosclerotic changes in the abdominal aorta, we have compared age trends of the aortic pulse wave velocity, measured by impedance plethysmography in normal subjects and in patients with coronary artery disease. Since arterial hypertension as well as age increases the pulse wave velocity,[1-6] only normotensive patients were selected for this series. Impedance plethysmography is a convenient method for inertia-free recording of the aortic volume pulse from skin electrodes and eliminates the necessity of intrapolation of records from the subclavian or carotid arteries as in earlier investigations.

We have also measured the interval from the earliest QRS deflection in any of simultaneous 3 standard electrocardiographic leads to the foot point of the aortic volume pulse recorded by impedance plethysmogram. This interval consists of the electrical latent period, the period of isometric contraction, and the time from the opening of the aortic valve to the arrival of the pulse wave in the vicinity of the aortic arch. The isometric contraction time is probably the most important of these components. The term "aortic ejection time" is used for abbreviation. The effects of age and of coronary artery disease on this interval was studied for the first time.

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Supported by Grant B 1859-C2, National Institutes of Health, U.S. Public Health Service.

Method

We used an impedance plethysmograph developed by Dr. O. H. Schmitt, Department of Biophysics, University of Minnesota.[7] With this instrument, variations of the base line due to varying blood content between a pair of electrodes are electronically eliminated. The record gives an inertia-free recording of the volume pulse due to variation of impedance in an alternating current circuit of 30,000 c.p.s., based on different conductivity of blood and surrounding tissue.

The aortic volume pulse was recorded from an electrode in the area of auscultation of the aortic valve with the second electrode opposite it on the back. Some exploration for the best location was needed, the chest electrode being varied slightly in the area of auscultation of the aortic valve. A satisfactory record could be obtained within a few minutes. The position of the back electrode was not critical. The tracings from the aorta were taken simultaneously with the 3 electrocardiographic standard leads on a 4-channel Sanborn recorder.

For the plethysmographic recording of the femoral pulse, one electrode was placed on the palpable femoral artery at the femoral triangle. The second electrode was placed opposite it on the thigh. The femoral pulse was also recorded simultaneously with electrocardiographic leads I, II, and III.

Impedance plethysmography is an indirect method; the calibration, in terms of units of electrical resistance (1/100 Ohm), cannot be converted into units of flow. This difficulty is not relevant to the present study, however, in which only the foot points of the aortic and femoral pulses were measured. The interval from the earliest QRS deflection in any of the 3 standard leads to the foot point of the aortic pulse ("aortic ejection time") and to the foot point of the femoral pulse was determined. The aortic pulse wave velocity (M./sec.) was calculated from the anatomic distance between the electrode positions, divided by the interval between the aortic and femoral pulse. The film speed was 50 mm./sec. (fig. 1).

Fifty-one healthy men were compared with 42 men with coronary artery disease. In the normal group, absence of detectable disease was assured

Table 1

Age Trends of Aortic Ejection Time in Normal Subjects and in Patients Recorded with an Impedance Plethysmograph

	Age group			
Normal subject	18 to 29	40 to 49	50 to 59	60 and over
N	18	12	16	15
M	0.087	0.098	0.103	0.109
S.D.	0.016	0.013	0.018	0.021
Coronary patient				
N	0	10	14	18
M	—	0.119*	0.122†	0.127†
S.D.	—	0.025	0.016	0.015

N, number; M, mean; S.D., standard deviation.

Time in seconds from the onset of the earliest QRS complex of standard limb leads to the foot point of the plethysmogram recorded at the aortic area.

*P <0.05.

†P <0.01.

by a thorough physical examination. All patients had a history of typical angina pectoris or infarction with abnormal resting electrocardiograms or abnormal electrocardiographic responses to exercise.* All subjects in both groups had a blood pressure of 140/90 or lower.

The age distribution of the 2 groups is shown in table 1. Only the age groups over 40 years can be compared (43 healthy men, 42 patients), since no patients with coronary artery disease under 40 years were available.

Results

Figure 2 shows the mean pulse wave velocity in comparable age groups of healthy men and of those with coronary disease. The lines with asterisks connecting the group means show the statistical significance of differences between age groups and the vertical lines show the statistical significance of differences between patients and normal subjects of the same age. The statistical significance was evaluated by means of the t-test (* $=p<0.05$; ** $p=<0.01$; *** $p=0.001$). The changes in the slopes of the curves are undoubtedly due to the relatively small number of subjects in each age group. The increasing pulse wave velocity in the normal men confirms previous results[1-6] and the validity of the method. The

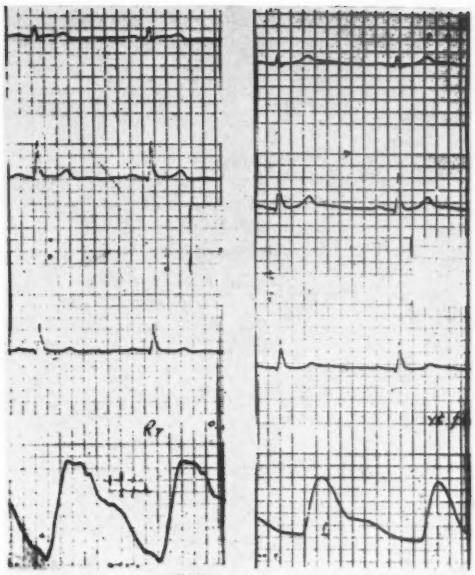

Figure 1

Impedance plethysmogram of the aorta (bottom, left) *and of the femoral artery* (bottom, right) *simultaneously taken with electrocardiographic leads I, II, and III.*

pulse wave velocity also increases with age in the patients with coronary disease, but the patients' values are higher in all age groups. The difference is greatest (and statistical significance highest) in the age group over 60. Since the age distribution in the healthy men and in the patients is similar, comparison of the mean values of the total groups over 40 is justified. It is 6.73 M./ sec. in the normal group, and 8.41 M./sec. in the patients. The difference of 1.68 M./sec. is statistically highly significant. If the curves are arbitrarily smoothed out and age differences for the same pulse wave velocity compared, an average difference of 18 years is found between the normal group and the patients.

Table 1 shows the means (M) and standard deviations (SD) of the "aortic ejection time" in the age groups of normal men and of patients with coronary artery disease. There is a slight continuous increase of the ejection time with age in the normal subjects as well

The patients were part of a group used for other studies by Dr. Henry Blackburn, Jr., at this Laboratory.

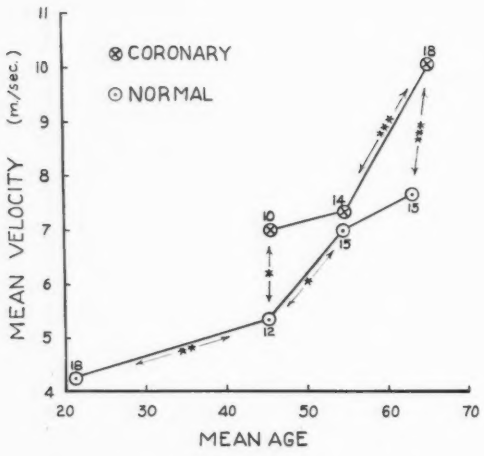

Figure 2

Increase of mean aortic pulse wave velocity in normal subjects and in normotensive patients with coronary disease with age. Lines with asterisks show statistical significance between age groups (= $p<0.05$; ** = $p<0.01$; *** = $p<0.001$). The aortic pulse-wave velocity is significantly higher in the patients.*

as in patients. The difference between the youngest and the oldest normal group is statistically highly significant ($p = <0.01$). The aortic ejection time is longer in all 3 age groups of patients than in the same normal age groups, and these differences are statistically significant.

Discussion

The higher aortic pulse wave velocity in patients with coronary disease than in normal men of the same age probably reflects degenerative changes in the aorta with resultant exaggerated age trends. It is possible that an increase of the aortic pulse wave velocity may precede coronary insufficiency, since the aorta is one of the earliest locations of atherosclerosis. In view of the simplicity of the method—the aortic and femoral impedance plethysmogram takes about the same time as a conventional electrocardiogram—it is suitable for large-scale clinical or epidemiologic exploration for early detection of atherosclerosis. The present study, though encouraging, is only the first step in this direction.

The "aortic ejection time" is physiologically not related to the pulse wave velocity but is presented for the sake of brevity, since the results were obtained with the same procedure on the same subjects.

Prolongation of the "aortic ejection time" with age cannot be due to the interval from the opening of the aortic valve to the arrival of the pulse wave beneath the electrode; the age trend of the aortic pulse wave velocity is opposite, and the time interval is too short to be measured with precision. We may also assume that the electrical latent period is fairly constant. The prolongation is therefore probably due to a prolongation of the isometric contraction time with age. This information could be directly obtained with cardiac catheterization, but impedance plethysmography has the great advantage of simplicity, and the avoidance of discomfort, inconvenience, or risk for the patient. The larger intervals in patients with coronary artery disease may be interpreted as some interference of the isometric contraction by myocardial ischemia or degeneration.

The changes of pulse wave velocity as well as those of the "aortic ejection time" in the patients with coronary artery disease are in the direction of normal age trends. This observation conforms, in general, to earlier experience in studies of peripheral circulation[6] and the electrocardiogram.[8]

Summary

Impedance plethysmograms were taken in 51 healthy men and 42 normotensive men with coronary heart disease from the aorta near the place of auscultation of the aortic valve and from the femoral artery in the femoral triangle recorded simultaneously with the 3 electrocardiographic standard leads.

The aortic pulse wave velocity was determined from the time interval between the foot points of the aortic and femoral volume pulse, and the anatomic distance between the electrodes. It increases with age in normal subjects as well as in patients, but the values are significantly higher in the patients. These re-

sults are suggestive of accelerated degenerative changes in the aorta, probably due to atherosclerosis.

The interval from the earliest detectable QRS deflection to the foot point of the aortic volume pulse ("aortic ejection time") becomes longer with age in the normal group. In patients with coronary artery disease, the prolongation is significantly larger for each of 3 age subgroups. The results suggest that ventricular ischemia affects ventricular isometric contraction.

Summario in Interlingua

In 51 homines normal e in 42 homines con normotension in le presentia de morbo coronari, plethysmogrammas de impedantia esseva obtenite ab le aorta proxime al sito de auscultation del valvula aortic e ab le arteria femoral in le triangulo femoral, in simultaneitate con le obtention del tres derivationes electrocardiographic standard.

Le velocitate del unda del pulso aortic esseva determinate super le base del intervallo de tempore inter le punctos de base del aortic e del femoral pulso de volumine, insimul con le distantia anatomic inter le electrodos. Iste velocitate cresce con le etate, tanto in patientes como etiam in normales, sed le valores es significativemente plus alte in le patientes. Iste resultatos suggere le presentia de accelerate alterations degeneratori in le aorta, probabilemente in consequentia de atherosclerosis.

Le intervallo inter le prime detegibile deflexion QRS e le puncto de base del pulso de volumine aortic ("tempore de ejection aortic") cresce con le etate in le gruppo normal e in le patientes, sed in istes—i.e. le gruppo de patientes con morbo de arteria coronari—le prolongation es significativemente plus marcate in tres sub-gruppos de etate. Iste resultatos suggere que ischemia ventricular affice le contraction isometric ventricular.

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Age

To be seventy years young is sometimes far more cheerful and hopeful than to be forty years old.—(To Julia Ward Howe on her seventieth birthday) By Oliver Wendell Holmes, M.D.

Pulmonary Vascular Volume, Resistance, and Compliance in Man

By WILLIAM R. MILNOR, M.D., ANTHONY D. JOSE, M.R.C.P., AND CHARLES J. McGAFF, M.D.

VARIATIONS in the volume of blood in the pulmonary vessels have been assumed to play a role in the physiology of the lesser circulation since the time of William Harvey,[1] but few measurements of the human pulmonary blood volume in vivo are available. This volume is an important variable in the hemodynamics of the pulmonary circulation because of the relationships between volume, pressure, and flow to be expected in an elastic system, which require that all 3 of these parameters be measured in order to interpret changes in any one of them.

In 19 patients with a variety of cardiac and pulmonary abnormalities we have made such measurements in the course of diagnostic catheterization of right and left heart chambers. The dye-dilution method was employed to measure cardiac output and mean transit time from pulmonary artery to left atrium, giving the data needed for calculation of pulmonary blood volume by the Stewart-Hamilton method.[2]

The results provide more direct measurements of pulmonary blood volume than have previously been available, and also give an estimate of relative vascular compliance. One limitation of the method is that it measures the characteristics of the entire pulmonary vascular bed, with no indication of the differences in volume, compliance, and resistance that exist among the arterial, arteriolar, capillary, and venous parts of the bed.[3] In spite of this limitation significant relationships between volume, flow, resistance, and compliance were found.

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Supported in part by grants from the American Heart Association, and from the National Heart Institute (H-328), U.S. Public Health Service.

Patient Selection and Methods

The patients studied were undergoing diagnostic catheterization of the left heart by the transbronchial[4] or percutaneous dorsal[5] route, and simultaneous right heart catheterization via an antecubital vein. The majority had rheumatic lesions of the mitral or aortic valve; individual diagnoses are listed in table 1. All gave a history of cardiopulmonary symptoms. None showed signs of congestive failure at the time of this study.

Patients were studied after fasting at least 4 hours, and were usually given 10 mg. of morphine sulfate intramuscularly, and in some cases 100 mg. of pentobarbital, 1 hour prior to the procedure. Measurements were made with the patient supine.

A no.-7 cardiac catheter was positioned in the pulmonary artery just beyond the valve by standard methods of intravenous right heart catheterization. The left atrium was catheterized with polyvinyl (I.D. 0.51 mm.) or polyethylene (I.D. 0.58 mm.) tubing passed through the puncture needle. Pressures were recorded by Statham P23-D or P23-A manometers* and a model DR-8 recorder.† Mean pressures were measured at end-expiration by electronic integration. The zero reference level for pressure measurement was a plane parallel to the top of the catheterization table, at a distance above it equal to two thirds the sagittal diameter of the thorax at the sternal angle.

Dilution curves from the brachial or femoral artery following injection of indocyanine green ("Cardiogreen")‡ were recorded by continuous sampling through a cuvette densitometer (Model 103).* The methods used for injection, sampling, recording, and calibrating have been described in detail elsewhere.[6]

When the catheters were in place and control blood samples were drawn, a dye injection was made into the left atrium and the arterial dilution curve was recorded. As soon as the primary curve was recorded, the sampling syringe was replaced, a new control blood sample was taken, and a pulmonary artery injection was made, with less than 5 minutes intervening between the 2 injections. Since the dye leaves the circulation rapidly, the

*Statham Instruments, Inc., Los Angeles, Calif.
†Electronics for Medicine, Inc., White Plains, N. Y.
‡Hynson-Westcott Company, Baltimore, Md.
*Colson Company, Elyria, Ohio.

Table 1

Summary of Results

Case no. and initials		Diagnosis	Age	Sex	Surface area ($M.^2$)	Heart rate (per min.)	Cardiac index ($L./min./M.^2$)	Mean pressure (mm. Hg) PA	Mean pressure (mm. Hg) LA	Blood volumes ($ml./M.^2$) V_{pa-a}	Blood volumes ($ml./M.^2$) V_{la-a}	Blood volumes ($ml./M.^2$) V_{pa-la}	PVR (RU/$M.^2$)	C	C_a
Patients with normal pulmonary vascular resistance															
1	E. J.	MS	52	M	1.90	84	2.84	21	20	897	570	327	0.3	16.0	—
2	E.H.	MI	53	M	1.97	60	2.57	14	12*	1217	652	565	0.8	43.5	—
3	V.S.	AI	19	F	1.60	90	3.28	15	11*	909	656	253	1.2	19.4	6.30
4	C.J.	AS	39	M	1.85	102	5.05	30	24*	794	371	423	1.2	15.7	4.83
5	M.P.	MS, AS, AI	37	F	1.51	86	3.25	30	23*	777	315	462	2.2	17.4	4.72
6	D.F.	MS	33	M	1.68	65	4.61	29	18*	1054	456	598	2.4	25.4	3.90
7	N.B.	My	63	F	1.59	110	2.88	25	17	548	422	126	2.8	6.0	2.21
8	B.K.	MS, AI	31	F	1.46	74	2.87	24	15*	789	463	326	3.1	16.6	1.47
9	Al.S.	MS, MI	35	F	1.50	102	5.15	33	16	1012	624	388	3.3	15.8	2.44
10	J.F.	MI	38	M	1.90	90	2.32	46	38	1335	1188	147	3.4	3.5	—
11	W.H.	MS, MI	51	M	1.71	86	3.00	31	19	1334	856	478	4.0	19.1	1.28
Patients with high pulmonary vascular resistance															
12	I.E.	MS, MI	50	F	1.58	93	2.81	38	23	750	352	398	5.3	13.1	3.64
13	O.T.	MS	38	F	1.70	58	3.48	37	16	856	363	493	6.0	18.6	1.46
14	An.S.	MS	34	F	1.68	111	4.44	62	29	761	301	460	7.4	10.1	0.42
15	L.G.	MS, MI	44	M	1.82	60	1.80	39	18*	1047	776	271	11.7	9.5	0.43
16	T.W.	MS	41	F	1.56	88	2.47	57	23	466	244	222	13.8	5.5	0.34
17	F.J.	MS, MI	42	M	1.69	124	1.94	47	18	909	639	270	14,9	8.3	0.21
18	M.W.	MS	40	F	1.54	76	2.81	69	24*	721	414	307	16.0	6.6	0.57
19	D.D.	PPH	24	F	1.54	97	4.04	84	2	687	260	427	20.3	9.9	0.05
	Means:						3.24			887	522	365			

*Indicates that left heart catheterization was by the percutaneous dorsal route.[5] The transbronchial route[4] was used in all other cases.

MS=mitral stenosis. MI=mitral insufficiency. AS=aortic stenosis. AI=aortic insufficiency. My=myocardial disease, etiology undetermined, probably secondary to coronary atherosclerosis. PPH=primary pulmonary hypertension. PA=pulmonary artery. LA=left atrium. Blood volumes by Stewart-Hamilton method: V_{pa-a}=pulmonary-left heart-arterial volume; V_{la-a}=left heart-arterial volume; V_{pa-la}=pulmonary blood volume. PVR=pulmonary vascular resistance. C=relative pulmonary vascular compliance (see text). C_a=pulmonary arterial compliance estimated by the method of Engleberg and duBois.[3]

control sample for the second-curve baseline was drawn immediately before the second injection. In a few cases the order of the injections was reversed. The total amount of blood withdrawn during the procedure varied between 50 and 100 ml.

Hematocrit levels were measured in Wintrobe tubes centrifuged for 30 minutes at 4,000 r.p.m. at 12-cm. mean radius. No correction was applied for trapped plasma. All blood volumes were calculated from plasma values and the arterial hematocrit values.

Cardiac output and mean transit time (MTT) were calculated from the dilution curves as described by Hamilton, Moore, Kinsman, and Spurling.[2]

The cardiac output calculated from left atrial injections was consistently higher than that calculated from pulmonary artery injection by a small but significant amount (mean difference 0.390 L. per minute, or 7.5 per cent of the output calculated from the pulmonary artery injection curve). This systematic difference has not been explained. The outputs from pulmonary artery injection were used in the present calculations.

The volume of the sampling system from needle tip to mid-cuvette was 0.35 ml., and the sampling rate was 0.6 ml. per second. The distortion of the arterial concentration curve by this system prolongs mean transit time by 0.6 second,[7] and this has been subtracted from the observed mean transit times. Since this prolongation affects the curves from both injection sites equally, the difference between their mean transit times, which represents pulmonary mean transit time, is not affected.

Dilution volume, or the volume of blood between sites of dye injection and sampling and all temporally equidistant points, was calculated by multiplying cardiac output per second by the appropriate mean transit time in seconds.[2] This volume has been given a variety of names in the past ("Q," "Stewart-Hamilton volume," "needle-to-needle volume," "central volume," etc.), but the term "dilution volume" has the advantages of descriptive accuracy and freedom from conflicting previous usage.

The following symbols are used:

Q = Cardiac output, in milliliters per second
MTT = Mean transit time, in seconds
V = Dilution volume, in milliliters

Subscripts following MTT or V indicate injection and sampling sites in that order:

PA = Pulmonary artery
LA = Left atrium
A = Brachial or femoral artery

Thus:

Pulmonary blood volume $= V_{pa\text{-}la} = (V_{pa\text{-}a}) - (V_{la\text{-}a}) = (Q)\ (MTT_{pa\text{-}a}) - (Q)\ (MTT_{la\text{-}a})$

Pulmonary vascular resistance (PVR) was calculated by dividing cardiac output in liters per minute into the pressure gradient from pulmonary artery to left atrium in millimeters of mercury:

$$PVR = \overline{P}_{pa} - \overline{P}_{la} \,/\, 60\ Q$$

The resulting expression gives PVR in resistance units (R.U.), which must be multiplied by 80.0 to convert to dyne sec. per cm.[5] The use of mean rather than instantaneous pressures and flows introduces an error unavoidable with present techniques, but the work of Engleberg and du Bois[3] suggests that the error may not be large.

Mean intravascular pressure in the pulmonary vascular bed ($\overline{P}_i$) was estimated by:

$$\overline{P}_i = \overline{P}_{pa} + \overline{P}_{la} \,/\, 2$$

This formula gives a rough estimate of the pressures acting to distend the pulmonary vascular bed, and would approximate mean transmural pressure if extravascular forces (intraalveolar pressure, tension in supporting structures) were negligible. Recent work by Riley, Permutt, Howell, and Proctor[8] suggests, however, that the extravascular forces may be of considerable magnitude. Pressure varies over the length of the pulmonary vessels, and P_i clearly underestimates the prearteriolar, and overestimates the postarteriolar pressures. Since our volume measurements include the entire pulmonary vasculature, however, it seems reasonable to use a mean intravascular pressure for the entire bed.

Relative Compliance (C) of the Pulmonary Vascular Bed

Our measurements represent one point on the pressure-volume curve of the lung vessels, and dividing pulmonary blood volume in milliliters by mean intravascular pressure in millimeters of mercury gives a figure (C) related to vascular compliance.

$$C = (V_{pa\text{-}la}) \,/\, \overline{P}_i$$

The conventional measurement of compliance by in vitro organ perfusion experiments requires measurement of the increase in volume per unit increase of pressure ($\Delta V/\Delta P$), but this is not readily applicable to man in vivo. The relative compliance, C, described above will be directly related to the true compliance $\Delta V/\Delta P$, if: (1) vessel lumen diameter depends only on net transmural pressure and the elasticity of the vessel walls, (2) P_i is an accurate measurement of net transmural pressure, (3) vessel length is constant, so that pulmonary blood volume is an index of average lumen diameter. Thickening of the vessel walls with no change in elasticity, for example, would modify the accuracy of assumption (1). The relation between C and $\Delta V/\Delta P$, like that between ΔV and ΔP, is probably nonlinear. Moreover, compliance changes in opposite directions in different parts

of the bed might cancel so as to be undetectable. If these limitations are kept in mind, the relative compliance may prove a useful comparative measurement.

To facilitate comparison of patients, all measurements of flow, volume, resistance, and compliance have been related to body surface area in square meters.

Results and Discussion

The results in each patient are listed in table 1. The mean pulmonary blood volume for this group of 19 patients was 365 ml. per M.^{2}, with individual values ranging from 126 to 598 ml. per M.^{2} These measurements, like those of Dock, Kraus, Woodward, Dexter, and Haynes,[9] who used a similar technic, are much smaller than previous estimates based on more indirect methods, which placed the pulmonary blood volume at 570 ml. per M.^{2} or more.[10-12]

The mean value for V_{pa-a} in our patients was 887 ml. per M.^{2}, approximately the same as that reported by other investigators for similar patients[13-16] (table 2). Borden, Ebert, and Wells[17] reported smaller values, but used *median* transit times in their calculations, which give slightly smaller volumes under these conditions than the correct values obtained with *mean* transit time.

V_{la-a}, on the other hand, averaged 522 ml. per M.^{2}, considerably larger than the radiologic estimate of 246 ml. per M.^{2} given by Lagerlof et al.[10] Since our measurements represent a more direct approach than has been available previously, it seems probable that earlier reports have underestimated V_{la-a} and overestimated pulmonary blood volume.

Although we have as yet no data on normal subjects, the volume between pulmonary artery and peripheral artery in patients with valvular heart disease, without signs of congestive failure, has been shown to be only slightly larger than that in normal subjects,[10, 13-17, 24] so that the normal values for pulmonary blood volume may not differ widely from those reported here.

Three possible sources of error in the present method should be mentioned. First, since the volume measured includes only blood that contributes to dilution of the dye, incomplete mixing in the left atrium would result in the inclusion of some portion of left atrial volume with pulmonary blood volume, and give falsely large estimates of pulmonary blood volume. It seems certain that atrial mixing is incomplete in some cases, but the magnitude of this error is unknown. Second, the portion of the systemic arterial tree included in V_{pa-a} and V_{la-a} is undetermined, and may vary in different patients and under different conditions. It seems safe to assume that this factor remains constant during the few minutes required for the 2 curves and is therefore not relevant to the measurement of V_{pa-la}. Third, the pulmonary blood volume must vary continuously throughout the cardiac and respiratory cycles, and the relation of these variations to the mean volume measured by this method has not been evaluated.

Table 2

Summary of Reported Values for Pulmonary, Left Heart, and Arterial Blood Volumes in Patients with Rheumatic Valvular Disease, not in Congestive Failure

References	Number of patients	Blood volumes (ml./M.^{2}) PA-A	LA-A	PBV
Borden et al. 1949[17]	10	642*	—	—
Lagerlof et al. 1949[10]	11	817	246†	571
Kopelman et al. 1951[13]	4	860	—	—
Doyle et al. 1953[14]	6	860	—	—
Rapaport et al. 1956[15]	16	805	—	—
Dock et al. 1959[9]	36	—	—	322
Milnor et al. (this report)	19	887	522	365

*Calculated from *median* transit times (see text).

†Estimated radiologically. All other values in this table were determined by indicator-dilution methods.

PA-A=pulmonary-left heart-arterial volume; LA-A=left heart-arterial volume; PBV=pulmonary blood volume.

Relative Compliance of the Pulmonary Vascular Bed

The absence of any correlation between the volume of blood in the pulmonary vessels and the pressure acting to distend them (P_i) suggests that there are real differences in pul-

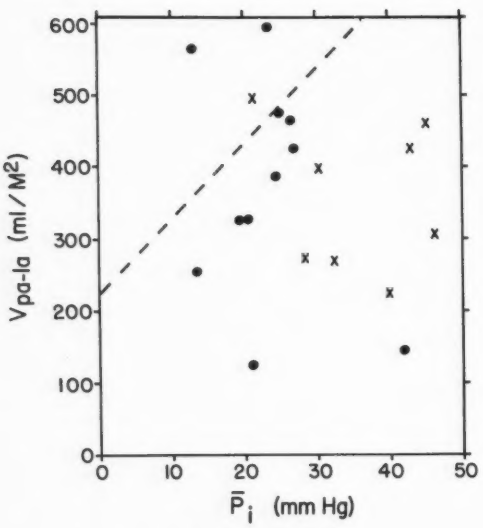

Figure 1

V_{pa-la} = pulmonary blood volume, in ml./M.² $\bar{P}_i$ = mean intravascular pressure in pulmonary vascular bed. The absence of correlation between these variables indicates that the patients studied differ in pulmonary vascular compliance. The broken line indicates assumed pressure-volume relationship with normal compliance. In this figure and in figure 2, (0) = patients with pulmonary vascular resistance < 4.0 R.U. per M.², (x) = patients with pulmonary vascular resistance > 4.0 R.U. per M.²

monary vascular compliance in our patients (fig. 1).

The relative pulmonary vascular compliance ($V_{pa-la}/\bar{P}_i$) averaged 14.7 ml. per M.², per mm. Hg when related to body surface area, or 0.408 ml. per Kg., per mm. Hg when related to body weight. If we assume a finite vascular volume at zero transmural pressure, absolute compliance must be smaller than our values. Engleberg and du Bois[3] found an average compliance of 0.214 ml. per Kg., per mm. Hg for the vascular bed of the isolated rabbit lungs, or about one half our average value. Extrapolation from their estimate of human pulmonary arterial compliance,[18] however, gives a value for the whole pulmonary vasculature that is almost equal to our mean relative compliance. If we assume as a first approximation that normal compliance lies somewhere between our relative compliance values and the in vitro determinations of Engleberg and du Bois,[3] e.g., 11.0 ml. per M.², per mm. Hg, and assume V_{pa-la} = 350 ml. per M.², $\bar{P}_i$ = 12 mm. Hg, and a linear relationship, the pressure-volume curve for the normal human pulmonary vascular bed would follow the line plotted in figure 1. All points below and to the right of this line would then represent decreased compliance.

Relation between Resistance and Compliance

Since resistance to blood flow through the lung could be controlled principally by changes in vessel diameter at a sharply localized level of the vascular bed such as the small arterioles, large changes in pulmonary vascular resistance could occur with little or no change in total pulmonary blood volume, and with no necessary relation between pulmonary vascular resistance and over-all compliance.

Our data nevertheless show a significant inverse correlation between these 2 variables ($r = -0.584$, $P < 0.01$). All but one of the patients with a high pulmonary vascular resistance (>4.0 R.U. per M.²) had relatively low total compliance (<15.0 ml. per M.², per mm. Hg), (fig. 2), suggesting that a generalized decrease in vascular distensibility either accompanies arteriolar narrowing or is itself responsible for the increased pulmonary vascular resistance in these patients.

This supposition is further supported by the finding that pulmonary arterial compliance (C_a) calculated from the pulmonary arterial pulse wave profile, cardiac output, and left atrial pressure by the method of Engleberg and du Bois[3] varies directly with our values for total pulmonary vascular compliance (fig. 2).

It is not possible to conclude whether the decreased compliance is due to vasoconstriction or to alteration in the structural elements of the vessel walls, both of which have been demonstrated in mitral stenosis.

The possibility that elevated P_{la} may invoke decreased over-all compliance independently of arteriolar effects is raised by 2 pa-

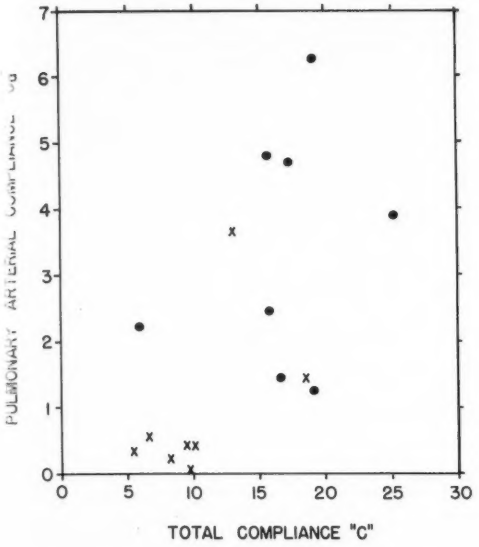

Figure 2

Ordinate. *Pulmonary arterial compliance, "C_a", estimated by the method of Engleberg and du Bois.*[3] Abscissa. *Relative compliance of the pulmonary vascular bed as a whole "C" (see text). On both axes compliance is expressed in ml. per M.², per mm Hg. Same patients as listed in table 1, less 3 cases whose "C_a" could not be calculated because adequate tracings of pulmonary arterial pressure pulses were not available.*

tients in our group who had very low compliance (< 10 ml. per M.², per mm. Hg) with normal pulmonary vascular resistance.

Relation between Flow and Volume

A direct correlation between cardiac output and pulmonary blood volume has been described by many investigators.[14, 15, 19, 20–22] A fall in pulmonary-left heart-arterial volume when cardiac output decreases under the influence of anesthetics, as described by Johnson[20] and by Etsten and Li[23] is consistent with this relationship, as is Ball, Kopelman, and Witham's finding that the "intrathoracic blood volume" increases with exercise.[24] In most studies in vivo[14, 15, 20] conclusions were based on measurement of pulmonary artery-to-peripheral artery volume, and the part played by left heart and arterial volume was uncertain.

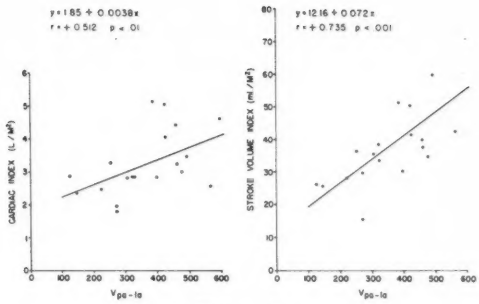

Figure 3

Correlations between pulmonary blood volume ($V_{pa\text{-}la}$) and cardiac index (graph on left), and between $V_{pa\text{-}la}$ and stroke volume index (right).

Johnson,[20] Sjostrand,[21] and Warren and Weissler,[25] using radiologic, plethysmographic, and indicator-dilution technics, found that pulmonary blood volume and heart volume were both correlated with cardiac output, but that the correlation with stroke volume was even closer than that with minute output.

Our data lead to the same conclusion, and show that the previously reported relationships were not due to variations in left heart volume alone. There was a significant positive correlation between pulmonary blood volume and cardiac index ($r = +0.512$, $p < .01$) and a closer correlation between pulmonary blood volume and stroke volume ($r = +0.735$, $p < .001$) (fig. 3).

The significance of this correlation can be questioned on the ground that cardiac output enters into the calculation of pulmonary blood volume.[14] As pointed out by Snedecor,[26] and by Rapaport and his colleagues,[15] however, correlation in such cases is not necessarily artificial. Analysis of the relation between $MTT_{pa\text{-}la}$ and cardiac index leads to the same conclusion, and the improved correlation when heart rate is introduced (in the calculation of stroke volume) suggests that the relationship is a real one.

The reason for this relationship is not clear. It would be expected in a simple elastic system of constant compliance and zero outflow pressure, where flow would be directly pro-

portional to perfusing pressure and volume directly proportional to pressure. This simple analogy cannot apply to our patients because compliance varied so widely in different subjects, and there was no significant relation between P_i and cardiac index.

A hypothesis consistent with our results is that the volume and distensibility of the pulmonary vascular bed directly influence the rate and extent of left atrial filling, and thus contribute to the regulation of left ventricular output. This concept is proposed by Sjostrand[21] and is closely related to Guyton's[27] view that "mean circulatory pressure," which is determined in part by the volume and distensibility of the vascular system, is an important factor in regulating cardiac output.

Summary

Pulmonary blood volume was measured in 19 patients, with use of a dye-dilution method and simultaneous bilateral cardiac catheterization. Pulmonary mean transit time was measured by subtracting left atrial-to-peripheral artery mean transit time from pulmonary artery-to-peripheral artery mean transit time.

Average pulmonary blood volume was 365 ml. per M.^{2} (range 126 to 598 ml. per M.^{2}). This value is significantly smaller than previous estimates by less direct methods.

The ratio of pulmonary blood volume to mean intravascular pressure was used as an indication of pulmonary vascular compliance. Patients with high pulmonary vascular resistance had relatively low pulmonary vascular compliance.

A significant correlation between pulmonary blood volume and stroke volume was found, lending support to the hypothesis that the volume and elasticity of the pulmonary vascular bed contribute to the regulation of cardiac output.

Acknowledgment

We acknowledge gratefully the cooperation of Drs. Henry Bahnson and Frank Spencer, who performed the left heart catheterizations, and the technical assistance of Miss Mary Lou Sparger and Miss Mary Ellen Horner.

Summario in Interlingua

Le volumine del sanguine pulmonar esseva mesurate in 19 patientes per medio de un methodo a dilution de colorantes e le effectuation simultanee de catheterismo cardiac bilateral. Valores medie pro le tempore de transito pulmonar esseva obtenite per subtraher le valores medie del tempore de transito ab le atrio sinistre ad le arteria peripheric ab le valore medie del tempore de transito ab le arteria pulmonar ad le arteria peripheric.

Le valor medie del volumine de sanguine pulmonar esseva 365 ml per m^2 de superficie corporee (con un minimo de 126 e un maximo de 598 ml). Iste valores significativemente plus basse que illo previement estimate per medio de minus directe methodos.

Le proportion de volumine de sanguine pulmonar a tension intravascular medie esseva usate como indication del resilientia pulmono-vascular. Patientes con alte resistentia pulmono-vascular habeva relativemente basse resilientia pulmono-vascular.

Esseva constatate un correlation significative inter le volumine del sanguine pulmonar e le volumine per pulso. Isto supporta le hypothese que le volumine e le elasticitate del vasculatura pulmonar contribue al regulation del rendimento cardiac.

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Symposium on Coronary Heart Disease
To Begin in August 1960 Issue

Successful External Electrical Defibrillation in Acute Myocardial Infarction

Report of a Case

By PHILIP R. NAST, M.D., CHARLES S. PENNYPACKER, M.D., AND JOSEPH A. WAGNER, M.D.

VENTRICULAR fibrillation is the most serious of all arrhythmias. It was first described in 1849 by Ludwig and Hoffa.[1, 2] Its presence even for a short interval is usually incompatible with life. With the onset of ventricular fibrillation there is an immediate cessation of circulation with a series of rapid irregular undulations that replace the coordinated contractions of the ventricle. These oscillations become gradually less marked until they cease altogether.

Ventricular fibrillation may occur in patients during anesthesia; in cases of drowning and electrocution; in Stokes-Adams attacks; in toxicity states due to drugs such as digitalis, quinidine, and procaine amide; during cardiac catheterization; terminally in ventricular tachycardia; and in coronary artery disease.

Sudden death due to coronary occlusion is by no means always in direct proportion to the extent of the infarction. Stroud and Feil[3] reported that in 50 per cent of the patients dying suddenly with coronary disease, death was due to a sudden paroxysm of ventricular fibrillation. Spontaneous recovery from ventricular fibrillation is rare although several cases have been reported including one in acute myocardial infarction.[4, 5]

The authors were fortunate enough to be in attendance at the bedside in the following case.

Case Report

A 45-year-old housewife and librarian was admitted to the Bryn Mawr Hospital on April 26, 1958, complaining of severe substernal chest pain. She was described as an apprehensive and tense individual with a history of transient labile hypertension. Her husband had died of a myocardial infarction several years prior to her admission.

On the afternoon of admission, while weeding in her garden at approximately 1:30 p.m., she suddenly experienced severe crushing anterior chest pain. Her physician arrived within 15 minutes and noted that the patient was pale, sweaty, slightly cyanotic, and pulseless. Heart sounds were barely audible and the blood pressure was 60/20. An injection of morphine sulfate 15 mg. and atropine sulfate 0.4 mg. relieved the pain somewhat and her pulse improved. She vomited copiously.

At 2:15 p.m. she arrived at the Bryn Mawr Hospital and still experienced anterior chest pain with some right arm pain; the blood pressure was 120/70. At 2:24 p.m. leads I, II, III, aV_R, aV_L, and aV_F of the recording electrocardiogram had shown changes diagnostic of a recent posterior myocardial infarction and chest lead V_1 was being recorded. At that moment the patient said, "Oh my, something's happening!" Within a few seconds she became unconscious, developed opisthotonus, and ceased to breathe. The heart sounds were inaudible. Clinically the patient appeared dead. The recording electrocardiogram showed ventricular fibrillation (fig. 1).

Nasal oxygen was started, the chest was pounded, and artificial respiration was attempted while the cardiac pacemaker and defibrillator were obtained from another floor. The electrocardiogram continued to reveal ventricular fibrillation during the 6-minute interval required to obtain the defibrillator and attach the electrodes externally to the patient's chest. Actually 4 minutes of ventricular fibrillation were recorded by the electrocardiogram. Short intervals during the 6 minutes were visually monitored but were not recorded (fig. 2). Three electric countershocks of 350 volts of 60-cycle alternating current of 0.15-second duration each were given at 10-second intervals at 2:30 p.m. with the Zoll-Electrodyne external defibrillator.*

From the Department of Medicine and the Service of Cardiology of the Bryn Mawr Hospital, Bryn Mawr, Pa.

Presented at the Eastern Pennsylvania Regional Meeting of the American College of Physicians, January 30, 1960, Philadelphia, Pa.

*Manufactured by the Electrodyne Company, Norwood, Mass.

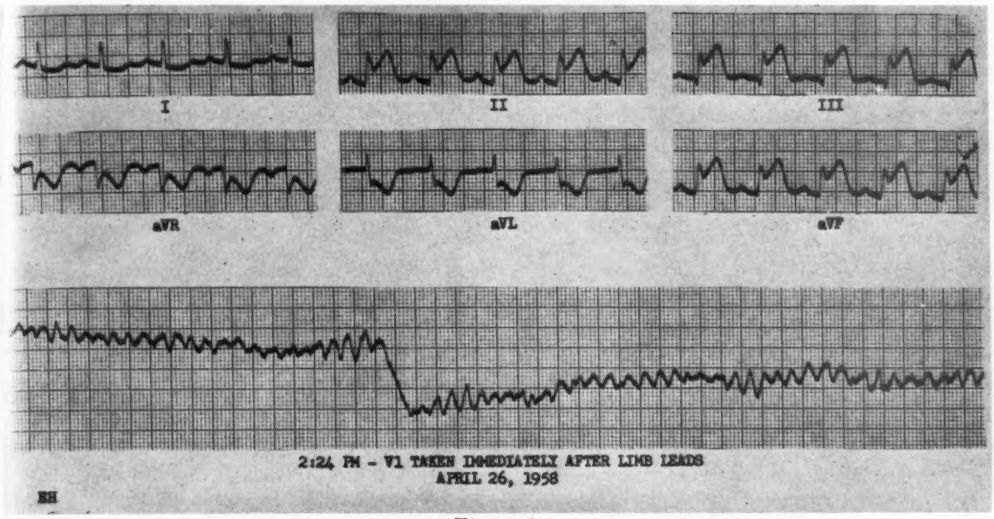

Figure 1

The 6-limb leads of the electrocardiogram were diagnostic of an acute posterior myocardial infarction. Lead V_1 taken at 2:24 p.m. revealed ventricular fibrillation.

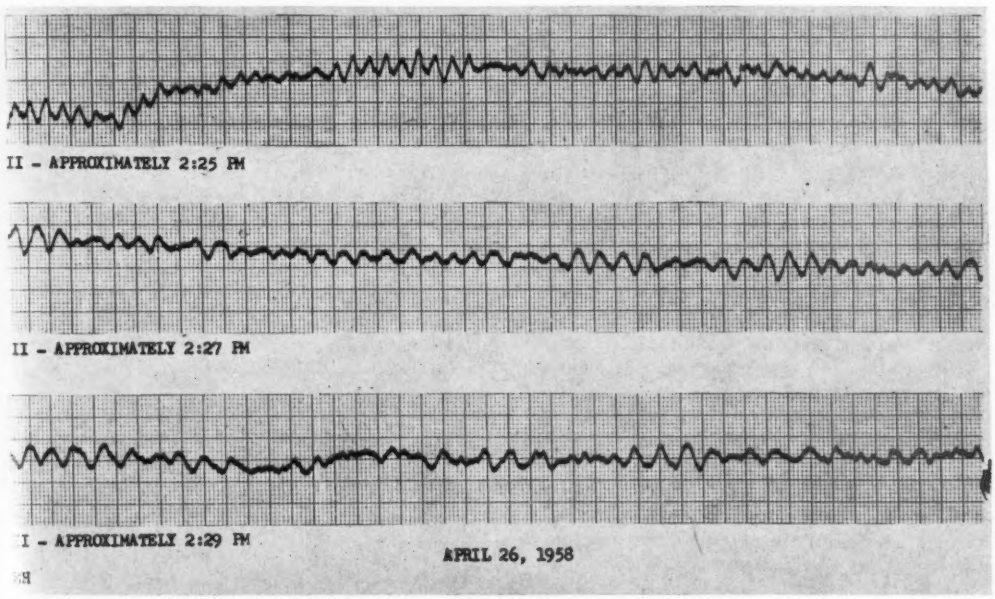

Figure 2

During the 6 minutes that ventricular fibrillation persisted, it was recorded on lead II. Representative segments of the tracing during this interval are shown.

The electrocardiogram about 1 minute later showed complete atrioventricular block and an idioventricular rhythm. At 2:32 p.m. the patient was in regular sinus rhythm (fig. 3) and had regained consciousness.

She was very apprehensive and at 2:38 p.m. vomited copious amounts of fluid. By 2:50 p.m. the apprehension had increased and numerous premature ventricular contractions were noted. She was given sodium amytal 250 mg. and procaine

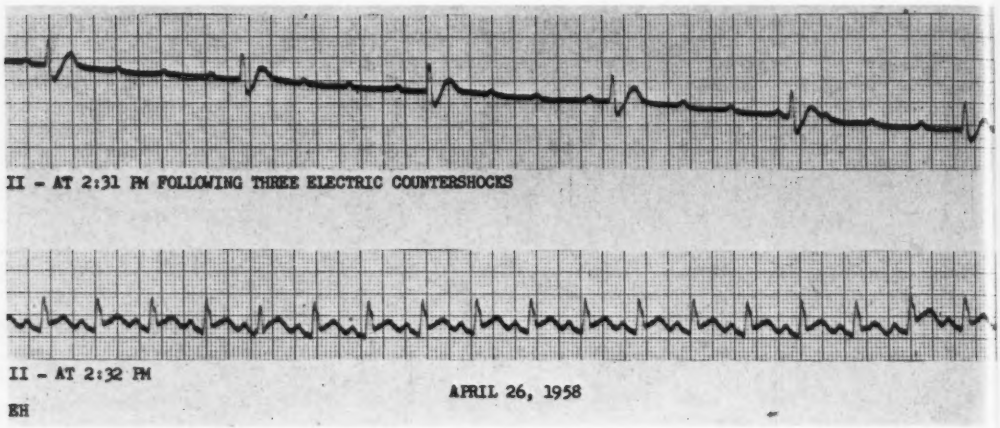

Figure 3

The heart was externally defibrillated with countershock at 2:30 p.m. Idioventricular rhythm was noted at 2:31 p.m., when the electrocardiogram was reconnected and regular sinus rhythm, was reestablished by 2:32 p.m.

amide 200 mg. intravenously at that time. The blood pressure was 152/110. The apprehension and premature contractions continued, and at 2:55 p.m. she was given morphine sulfate, 10 mg. hypodermically. At 3:05 p.m. atropine sulfate, 0.4 mg. hypodermically, and quinidine gluconate, 200 mg. intramuscularly, were administered, the blood pressure then being 114/90. Soon the apprehension and premature contractions diminished and the patient's condition became less critical. The pulse, which was 120 immediately following restoration of regular sinus rhythm, fell to levels of 88 within 1 hour. The patient was quite talkative during the few hours after regular sinus rhythm had been restored.

The atropine was continued every 6 hours for the first day only, and quinidine 200 mg. by mouth every 6 hours was continued for weeks. The patient vomited small amounts frequently during the first few hours and the temperature rose to 101 F. She was given intramuscular penicillin. The temperature was normal within 3 days. Serial tracings were diagnostic of a posterior myocardial infarction (fig. 4). Except for a leukocytosis of 14,400 with a normal differential count, a sedimentation rate of 22 mm. per hour, and a serum cholesterol of 292 mg. per cent the routine laboratory studies were normal.

Anticoagulant therapy was delayed 48 hours lest a hemorrhagic pericarditis develop secondary to electrical burns from the shocks. Her skin continued to be pale gray for about 4 days, but gradually improved. Although she spoke coherently during the first 4 days of her hospitalization, she has an amnesia for events that occurred during that time. Two circular first-degree burns outlining the area where the electrodes were applied were noted; these healed by the sixth day.

The patient was discharged on May 28, 1958, 32 days after admission. The remainder of her convalescence was uneventful. There have been no motor or sensory defects noted in this patient, either while in the hospital or since her discharge. The patient's ventricular fibrillation continued for 6 minutes and her unconsciousness continued for 8 minutes. She returned to her employment as a school librarian in September 1958 and except for some anterior chest discomfort that occurs with excitement is otherwise well (fig. 5).

Discussion

It is important to be aware that ventricular fibrillation may be the cause of so-called "sudden death" in patients with acute myocardial infarction. Promptly distinguishing this arrhythmia from cardiac standstill by means of the electrocardiogram and immediate treatment may result in successful resuscitation. Delay constitutes the major limitation in achieving success. External defibrillation seems more feasible in the treatment of ventricular fibrillation in coronary occlusion, since thoracotomy with cardiac massage in this age group could of itself prove fatal. At

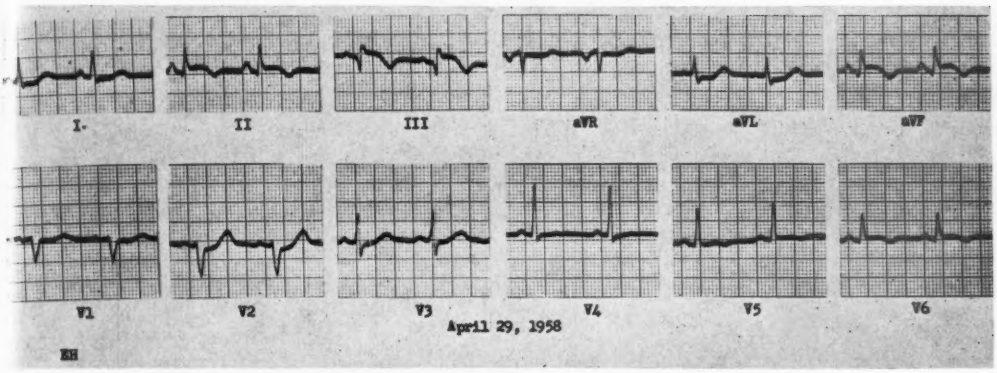

Figure 4

The electrocardiogram 3 days after defibrillation showed a maturing posterior infarction.

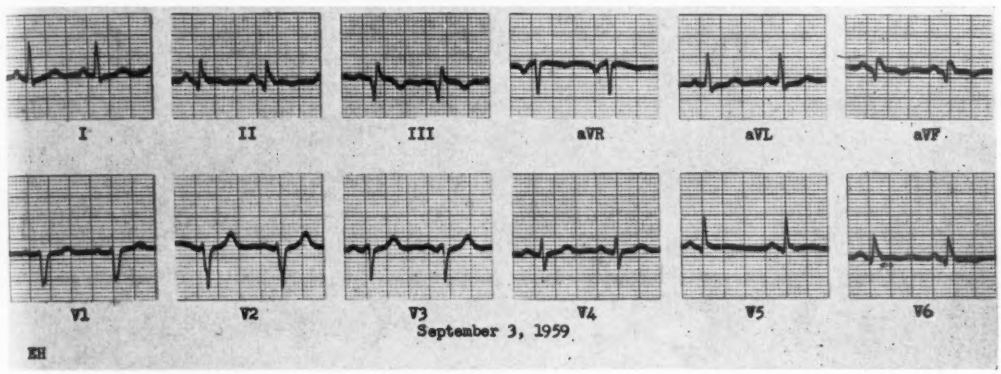

Figure 5

The electrocardiogram 16 months after defibrillation is compatible with an old posterior myocardial infarction.

least 5 cases of ventricular fibrillation in acute myocardial infarction are reported, however, that were treated by thoracotomy and cardiac massage and then by direct defibrillation with survival.[6-9] Our own experience in treating 8 such patients by thoracotomy, cardiac massage, and direct defibrillation of the heart did not result in the survival of any patient for more than 13 hours; although in a few instances regular sinus rhythm was restored, shock and unconsciousness persisted in all to death.

Historically the first successful defibrillation by countershock was performed by Prevost and Batelli on the exposed dog heart in 1899.[10, 11] Hooker et al.,[12] Wiggers,[13] and Guyton and Satterfield[14] showed that currents if strong enough could successfully defibrillate the heart through the unopened chest and that 60-cycle alternating current was the most satisfactory. Beck, Pritchard, and Feil were the first to terminate ventricular fibrillation in man by the direct application of countershock current to the heart through the opened chest.[15] Zoll and his group were the first to terminate ventricular fibrillation in man by the external application of countershock current across the unopened chest.[16] Zoll and Kouwenhoven and his group have devised instruments to be utilized externally in the treatment of patients with this arrhythmia.[16, 17]

Experimentally, high voltage, rapid successive shocks without adequate rest periods have produced cardiac damage as manifested by abnormal QRS complexes, decreased blood pressure, spontaneous recurrent ventricular fibrillation, and actual thermal destruction of muscle.[18] Zoll, however, reported no untoward effects with countershock in numerous animals and no evidence of damage to the hearts in 3 patients autopsied who had been defibrillated multiple times.[18, 19]

There are at least 2 cases in children of ventricular fibrillation lasting as long as 24 and 45 minutes that were successfully defibrillated with survival. Both these cases, however, occurred in the operating room where immediate massage maintained the circulation until regular sinus rhythm was restored.[15, 20] Levine and Matton reported a case of ventricular fibrillation followed by asystole lasting 5 minutes in a patient with Stokes-Adams disease who recovered after the intracardiac injection of epinephrine.[21]

Experimentally, Weinberger et al. showed that if circulation was interrupted in cats for over 3 minutes 25 seconds that some permanent damage to the central nervous system occurred. No cat survived when circulation was interrupted over 8 minutes 45 seconds.[22] Our case had no detectable defect after 6 minutes of interrupted circulation except for the persistent amnesia for events of the first 4 days of hospitalization. The amnesia may at least in part be due to the sedation as the memory loss began with the initial injection of morphine prior to admission.

External defibrillation has been successful with patients surviving in cases of ventricular fibrillation occurring during cardiac catheterization, in drug toxicity, and in Stokes-Adams attacks.[16, 17, 19, 23, 24] Patients with acute myocardial infarction and ventricular fibrillation have been externally defibrillated a number of times but defibrillation resulted in either ventricular standstill that did not respond to external cardiac pacemakers or recurrent ventricular fibrillation and death.[16]

We have been unable to find another case of acute myocardial infarction with ventricular fibrillation that has been restored to regular sinus rhythm with external defibrillation and survived. It is unlikely that a patient with this catastrophe will often be observed within the time permitting resuscitation. We were fortunate that circumstances prevailed permitting success in this case.

Summary

A patient with an acute myocardial infarction was observed who gave all the appearances of being dead; the electrocardiogram attached at the time showed ventricular fibrillation, which persisted for at least 6 minutes.

Regular sinus rhythm was restored within 2 minutes after external defibrillation with the Zoll-Electrodyne External Defibrillator with use of 60-cycle alternating current at 350 volts every 10 seconds for 3 shocks.

No other similar case that survived has been found in the literature.

The necessity of immediate recognition of ventricular fibrillation in acute myocardial infarction is pointed out in cases of "sudden death."

The preference of external electrical defibrillation over direct heart defibrillation is discussed.

Summario in Interlingua

Esseva observate un patiente con acute infarcimento myocardial qui exhibiva omne signos de esser morte. Le electrocardiogramma in progresso a ille tempore monstrava fibrillation ventricular que persisteva durante al minus 6 minutas.

Un regular rhythmo sinusal esseva restaurate intra 2 minutas per medio de disfibrillation externe effectuate con le apparato Zoll del compania Electrodyne, utilisante un currente alternante de 60 cyclos a 350 volt e applicante un triple choc a intervallos de 10 secundas.

Nulle simile caso, con superviventia del patiente, se trova in le litteratura.

Es signalate le necessitate de recognoscer fibrillation ventricular in acute infarcimento myocardial in casos de "morte subitanee."

Le avantages del externe disfibrillation electric es discutite in comparation con le directe disfibrillation del corde.

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Pericardial Effusion, a Manifestation of Systemic Lupus Erythematosus

By STANLEY S. BERGEN, JR., M.D.

PERICARDIAL effusion can be a striking physical and radiologic finding, but its occurrence as a manifestation of disseminated lupus erythematosus has not been emphasized. During the last 2 years 4 patients with systemic lupus erythematosus who had an associated pericardial effusion were seen at this hospital. Two of this group were misdiagnosed and treated incorrectly, partly because of failure to consider lupus erythematosus as a cause of pericardial effusion.

Case Reports

Case 1

A 39-year-old Negro cook was admitted to St. Luke's Hospital with swelling of hands and feet and left-sided chest pain for 3 months. He stated that he had been hospitalized for 6 weeks while in military service with joint pains and "glandular enlargement." He had also been hospitalized elsewhere 18 months previously following 3 months of left anterior chest pain, fever to 104 F., night sweats, joint pains, and weight loss of 15 pounds. The hospital record noted generalized lymphadenopathy, a hemoglobin of 11.2 Gm. per cent, electrocardiographic "evidence of pericarditis," and an enlarged heart compatible with pericardial effusion, and bilateral pleural thickening. Despite negative cultures of sputum and gastric aspirate, he was treated with Isoniazid and streptomycin with apparent improvement. He left the hospital against advice before therapy was completed. He then felt well, but a year before admission to St. Luke's hospital he noted intermittent swelling and pain in the proximal interphalangeal joints.

Four months before hospitalization he had a 6-day episode of fever, and a chest x-ray disclosed peribronchial infiltration, both of which cleared without specific therapy. Three months before admission an epitrochlear lymph node biopsy revealed "chronic inflammation." Thereafter he experienced dyspnea on effort, paroxysmal nocturnal dyspnea, ankle and hand swelling, joint pain, and "feverishness."

From the Department of Medicine, St. Luke's Hospital, New York, N.Y.

On physical examination he appeared well nourished and in no distress. The blood pressure was 120/80, there was no clubbing, the heart was not enlarged, the lungs were clear, and the abdomen contained no masses or enlarged organs. There was generalized lymph node enlargement and swelling of all the proximal interphalangeal joints of the hands.

Laboratory data included a normal urinalysis, hemoglobin of 10.1 Gm. per cent, white blood cell count of 9,900 per mm.^{3} with a normal distribution, negative serologic test for syphilis, thymol turbidity of 9.2 units, serum albumin of 3.4 and serum globulin of 6.4 Gm. per cent, the electrophoretic pattern showing the gamma globulin to be over 50 per cent. Latex fixation test was normal; all cultures (sputum, gastric, and urine) for tuberculosis were negative, and the bone marrow was within normal limits with negative LE preparation. A sickle-cell preparation was negative and an electrocardiogram was within normal limits. Two of LE preparations done on venous blood were positive, as was the LE precipitin test. Chest x-ray disclosed a heart of normal size, calcific left hilar lymph nodes, and linear strand densities at the right base and left mid-lung. Skin tests for blastomycosis, coccidioidomycosis, histoplasmosis, and lymphogranuloma venereum were negative. The Mantoux test was positive at 1:1,000 dilution.

Cardiopulmonary study revealed a defect in aeration with arterial unsaturation on exercise, reduced vital capacity and minute hyperventilation at rest, and low bicarbonate serum level. These findings were believed compatible with pulmonary fibrosis and an early diffusion block. Lymph node, skin, and muscle biopsies did not reveal any specific lesions, although perivascular clusters of lymphocytes and plasma cells were noted. Evidence of tuberculosis or Boeck's sarcoid was not seen. Following spontaneous clearing of his chest pain, the patient was given chloroquine, 250 mg. 3 times a day, with marked improvement in his joint pain and swelling.

The patient has been seen in the clinic for the last 18 months with intermittent exacerbations of joint pain. LE preparations have been repeatedly positive and he has required hospital admission on 2 occasions for prednisone therapy for relief of joint pain and febrile exacerbations. He is at present doing well on chloroquine and is believed

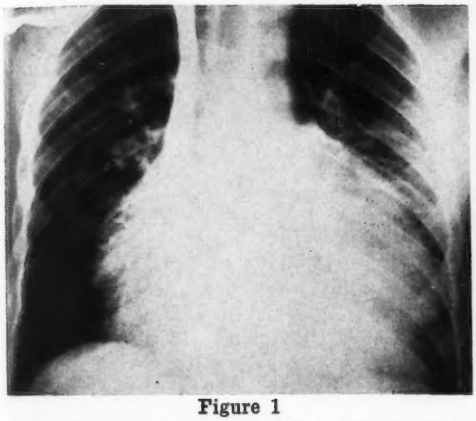

Figure 1

Angiocardiogram in case 2, revealing pericardial effusion.

Figure 2

Posteroanterior roentgenogram of the chest 4 months after pericardiocentesis in case 2.

to have disseminated lupus erythematosus with associated pulmonary fibrosis of undetermined etiology.

Case 2

A 29-year-old Negro merchant seaman was transferred to St. Luke's hospital for surgery. He had been hospitalized elsewhere 3 months previously following a 6-week history of knee, ankle, and hand pain. During this period the patient had also noted urinary frequency and a cough productive of small amounts of yellow mucoid sputum. Five years earlier the patient had been hospitalized for fever that disappeared spontaneously.

On physical examination the blood pressure was 150/90 mm. Hg, and the patient had a markedly puffy face with edema of the eyelids. There was a macular eruption over his forehead, face, and nose that had a "butterfly" distribution. The heart sounds were quiet, the heart seemed enlarged, and no murmurs were heard. Bilateral basilar rales were heard, and there was edema of ankles and wrists.

Laboratory data included a negative serologic test for syphilis, thymol turbidity of 18 units, hemoglobin of 11.9 Gm. per cent, white blood cell count of 4,050 per $mm.^3$ with a normal differential count, serum albumin of 3.2 and serum globulin of 5.1 Gm. per cent. An electrocardiogram showed low voltage and a chest x-ray showed a large cardiac silhouette probably due to pericardial effusion, with minimal bilateral pleural effusions. LE preparations were repeatedly positive.

A diagnosis was made of systemic lupus erythematosus and the adrenal steroid therapy was started. Venous pressure at that time was 176 mm. of saline and the arm-to-tongue circulation time (Decholin) was 14 seconds. Symptoms and physical findings improved during the subsequent month, the steroid dosage was reduced, and chloroquine 250 mg. twice daily was added.

Nevertheless the cardiac shadow increased in size, despite unchanging venous pressure levels; therefore, pericardiocentesis and pericardial biopsy were recommended and the patient was transferred to St. Luke's hospital where LE preparations of the blood were again positive, and an electrocardiogram revealed inverted T waves in leads I, II, aV_F, and V_{4-6}. An angiocardiogram confirmed the presence of a pericardial effusion (fig. 1).

An open pericardiocentesis and pericardial biopsy were performed and 600 ml. of straw-colored fluid were aspirated and clotted quickly. All cultures and LE-cell preparations on this fluid were negative. The biopsy showed dense fibrous tissue and a few scattered lymphocytes. The chest wound drained pericardial fluid for about 10 days and then closed. The cardiac size returned toward normal after a few days. The venous pressure fell to 70 mm. of water, whereas the arm-to-tongue circulation time remained at 14 seconds.

Following surgery, the dosage of prednisone was gradually reduced, and maintenance therapy with chloroquine was reinstituted. Now, 20 months later, the cardiac examination, chest x-ray (fig. 2), and electrocardiogram are normal. The patient is working as a merchant seaman and he is asymptomatic except for mild joint pain that is responsive to aspirin.

Case 3

A 37-year-old Negro woman was first admitted to St. Luke's hospital 3½ years ago with multiple joint pains. At that time she had discrete areas

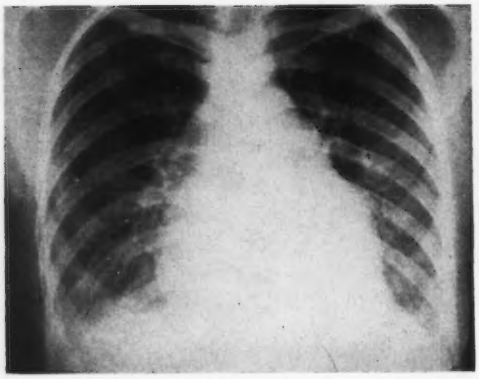

Figure 3

Case 3. Roentgenogram of the chest, showing probable pleural and pericardial effusions.

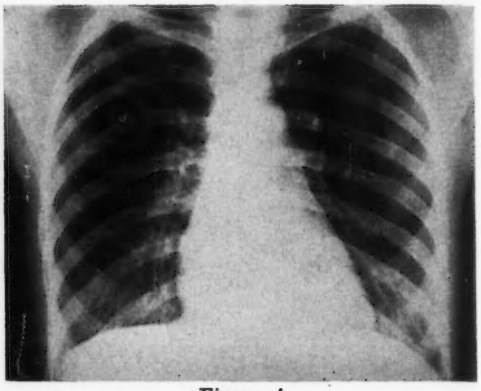

Figure 4

Roentgenogram of the chest in case 3 after 4 weeks of intensive therapy.

of hyperpigmentation over the trunk and extremities, generalized lymphadenopathy, and splenomegaly. Pertinent laboratory data revealed depressed blood platelet counts, reversal of the normal albumin/globulin ratio, positive Mazzini and Kahn tests, negative VDRL, and positive LE-cell preparations. On aspirin and prednisone all symptoms cleared and the blood platelet counts returned to normal.

Approximately 6 months later she was re-admitted to the hospital because of severe joint pain, anemia, and thrombocytopenia. She improved on prednisone and, as the dosage was reduced chloroquine was begun with maintenance of improvement. During this exacerbation a left pleural effusion and a splenic infarct occurred, both of which improved by time of discharge.

A third admission 1 year later was prompted by ataxia and confusion that cleared when chloroquine was stopped. Three weeks later she suffered severe right upper abdominal pain. The temperature was 100.8 F., the heart seemed enlarged, a grade II apical systolic murmur was heard, and a tender liver edge was felt below the right costal margin. Laboratory studies showed 4+ albuminuria, hemoglobin of 9.6 Gm. per cent, white blood cell count of 7,900 per mm^3., serum albumin of 2.7 and serum globulin of 4.2 Gm. per cent. An electrocardiogram revealed low voltage and inverted T in leads II, III, aV_F, and V_{3-6}. A chest x-ray was consistent with pericardial effusion and a small right pleural effusion (fig. 3). Transiently on the third hospital day pleural and pericardial friction rubs were heard. The congestive failure improved following digitalis and diuretic therapy. An increase in prednisone dosage led to improvement of joint pains, skin rash, and gradual resolution of the effusions over a 4-week period (fig. 4). The pulse pressure did not fall below 20 mm. of Hg, nor did the venous pressure exceed 170 mm. of water. The patient has not been seen since discharge.

Case 4

A 13-year-old Negro school girl was admitted to St. Luke's hospital with joint pains, fever, and a diffuse maculopapular scaling skin rash for 1 week following a sore throat. Physical examination revealed tachycardia of 120, a grade II, apical systolic heart murmur, and multiple warm, tender, swollen, slightly erythematous joints. An electrocardiogram disclosed the Wenckebach phenomenon. The white blood cell count was 5,400 per $mm.^3$, the hemoglobin was 9.0 Gm. per cent, and chest x-ray revealed an enlarged globular heart compatible with pericardial effusion (fig. 5).

The patient was believed to have acute rheumatic fever with myocarditis, pericarditis, and pericardial effusion. She was given 40 mg. of prednisone a day and as she improved and her electrocardiogram reverted toward normal, the dose was gradually reduced. Because of the skin rash and hematologic findings, LE preparations were made, which were positive on many occasions.

Prednisone treatment was continued, but the patient has never been completely free of fever and joint pain. Despite intensive therapy she has experienced 3 exacerbations of her disease. The pericardial effusion gradually resolved over a 3-month period (fig. 6). At present she is fairly well controlled on methyl-prednisolone and chloroquine but retains an extreme "Cushingoid" appearance.

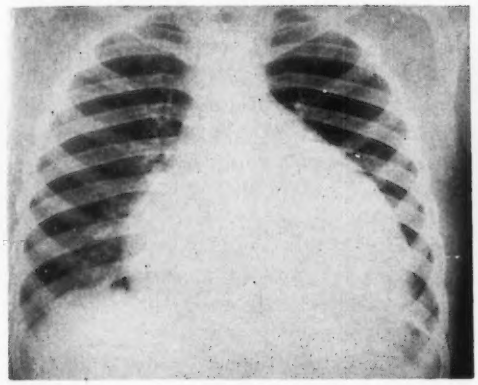

Figure 5
Posteroanterior roentgenogram of the chest in case 4, showing enlargement of cardiac silhouette.

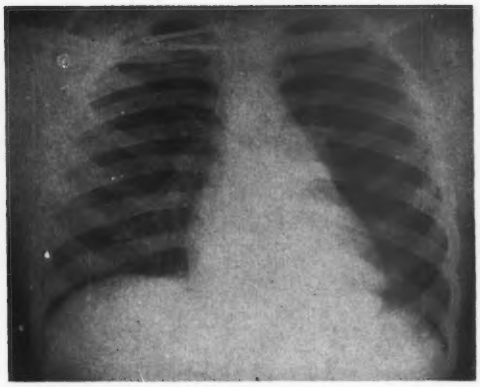

Figure 6
Posteroanterior roentgenogram of the chest in case 4 after remission of the lupus erythematosus.

Discussion

Four patients with a pericardial effusion, as a major manifestation of lupus erythematosus disseminatus were encountered. In 2 instances, the significance of the effusion was misinterpreted and in 1 an incorrect diagnosis was made. In the latter instance, proper therapy was delayed for 18 months.

That all 4 patients were Negroes is noteworthy, since less than 30 per cent of the general clinic population of St. Luke's hospital is Negro. That 2 of the patients are men is also striking. Two of the group are doing well and the third has been reported to be free of complaints without medications. Only the youngest patient seems to be doing poorly; in her case side effects of therapy are proving as difficult as her disease.

Many of the clinical and laboratory manifestations of lupus erythematosus were seen in these patients. No correlation of symptoms, physical findings, or laboratory tests would predict the development of pericardial effusion. The usual physical findings and electrocardiographic evidence of pericardial disease were present but were similar to findings in pericarditis and effusion of any etiology.

Review of Literature

In 1924 Libman and Sacks[1] described the valvular and endocardial manifestations of lupus erythematosus. Eleven years later Christian[2] reported a syndrome that included inflammation of serous membranes, and the same year Baehr, Klemperer, and Schifrin[3] noted the association of a diffuse vascular disease with lupus erythematosus.

Jarcho[4] reiterated that lupus erythematosus was a generalized vascular disease and reported 1 case of loculated pericardial effusion and another case with pericardial adhesions. In 1938 acute disseminated lupus erythematosus was reported in 2 patients who had hydropericardium.[5, 6] Contratto and Levine,[7] in 1939, reported a case of acute lupus erythematosus with a pericardial friction rub and pericardial fluid. They noted the similarity of their case to cases of acute rheumatic fever, including a prolonged P-R interval. The association of verrucous endocarditis and pericardial fluid in acute lupus erythematosus was described by Blount and Barrett[8] in 1945.

Klemperer, Pollack, and Baehr[9] reviewed 35 cases of disseminated lupus erythematosus and concluded that the diffuse connective-tissue lesion and its progressive degenerative nature were indicative of a sensitivity reaction. This idea received support from a report by Fox[10] of a patient who received antitetanus serum and developed lupus erythematosus.

In other reports an association was noted of allergic reactions and pericardial abnormal-

ities, both clinically[11, 12] and experimentally.[13] This hypothesis has been further developed by Dameshek,[14] who referred to systemic lupus erythematosus as "a complex auto-immune disorder."

Klemperer et al.[9] noted the frequent occurrence of fibrinous pericarditis in lupus erythematosus, and a few years later Aegerter and Long[15] called attention to the multiple mesenchymal lesions and serous effusions of the collagen diseases. In 1949 Curtis and Horne[16] described what they believed were the first reported cases of lupus erythematosus with pericardial effusion as the main manifestation. One of their 2 patients underwent repeated pericardiocentesis for relief.

Recently there have been many reports of pericarditis as a manifestation of lupus erythematosus,[17–24] with the incidence varying from 18[23] to 50 per cent.[24, 25] Acute pericardial effusion has been noted less frequently,[18, 20, 22, 23, 25–27] with an incidence of 8[26] to 18 per cent.[23] Most of the effusions were small, but occasionally were massive.[20, 22, 23, 25, 28, 29] Pericarditis has also been noted in discoid lupus.[30] Harvey et al.[28] emphasized that pericardial involvement usually occurs during an acute exacerbation of the illness.

The most common manifestation of pericardial involvement seems to be pericardial rub[7, 22, 23, 25–28, 31, 32] with chest pain,[22, 25, 28, 32] gallop,[28, 31] electrocardiographic changes,[7, 8, 16, 22, 23, 25, 28, 32] cardiomegaly,[16, 25, 33] cardiac failure,[28, 31, 33] and arrhythmias[28] also being noted. In most cases of lupus erythematosus adhesive fibrinous pericarditis is found at autopsy[7, 8, 9, 16, 17, 19, 23, 27, 29, 34, 35] although Harvey et al.[28] reported 2 cases of purulent pericarditis. No instance of constrictive pericarditis has been reported thus far,[25, 28] but tamponade has been noted.[16, 22, 23, 25] The fluid does not have any special characteristic[22, 25] and has been variously described as turbid,[5, 34] serosanguineous,[28, 29] clear brown,[7] and clear, pale yellow.[16] The amount varies from a few cubic centimeters[3, 36] to 3 liters,[24] with some cases requiring pericardiocentesis for relief.[16, 23, 24, 32] In at least 3 cases typical LE cells have been demonstrated in the pericardial fluid.[22, 32, 37]

Radiologic reviews of the x-ray manifestations of lupus erythematosus usually mention pericardial effusions.[20, 38] The differentiation between acute cardiac dilatation and pericardial effusion is often difficult and is frequently resolved only by angiocardiography.[20, 39, 40] Pericardial biopsy may also be helpful.[41–44]

It is well known that lupus erythematosus is rare in men,[14, 28] and at one time it was felt to be rare in non-Caucasian races.[28] An incidence in Negroes in larger series[26] belies this impression and is close to the incidence of Negroes in the general population.[45] Of the 5 case reports of lupus in the male Negro[4, 27, 34, 36] (as is true of the 2 Negro men in this report) pericardial involvement with effusions of various quantities was present in all.

The occurrence of false-positive serologic tests for syphilis, as noted in case 3 of this group, has been well documented in from 15[26] to 44 per cent[45] of patients with lupus erythematosus. The treponema pallidum immobilization test can be used for differentiation from actual syphilis if necessary.[46]

Since 3 of the 4 cases in this report were initially misdiagnosed and 2 were incorrectly treated, a greater awareness of pericardial effusion as a possible manifestation of lupus erythematosus may be needed. McKusick and Harvey[25] and McCuiston and Moser[22] have suggested that many so-called idiopathic or nonspecific cases of pericarditis are actually cases of lupus erythematosus. In many reports idiopathic pericarditis is considered a sensitivity[47, 48] or immune reaction.[49] If this possibility is kept in mind, a greater effort to secure tissue or bacteriologic proof is needed before pericarditis is arbitrarily considered to be idiopathic, viral, or tuberculous in origin. A recent review[22] reveals the similarities and dissimilarities between idiopathic pericarditis and the pericarditis of lupus erythematosus. Awareness of urinary, hematologic, skin, and serum protein changes will help in the differentiation of these 2 types of pericarditis. Angiocardiography, pericardiocentesis, and peri-

cardial biopsy may aid in making the correct diagnosis.

Medically, the treatment of choice is administration of the adrenal steroid hormones[18, 31, 32] with whatever maintenance dosage is needed to avoid recurrence. Surgically, pericardiocentesis may prevent tamponade, and in refractory cases, such as case 1, actual open drainage or pericardiopexy may be useful.[31]

Summary

Four cases of systemic lupus erythematosus with pericardial effusion as a prominent manifestation are reported. Lack of awareness of this finding as a not infrequent part of the disease entity led to misdiagnosis in 2 instances and incorrect treatment in 1. The literature on the subject is reviewed and suggestions are offered for diagnosis.

Summario in Interlingua

Es reportate quatro casos de systemic lupus erythematose con effusion pericardial como manifestation prominente. Non-recognition del facto que effusion pericardial es un elemento non infrequente in le tableau clinic de systemic lupus erythematose esseva le causa de un misdiagnose in duo del casos e de un incorrecte forma de tractamento in un. Le litteratura concernite con iste thema es revistate. Suggestiones pro le diagnose es offerite.

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Vitamin E

Effect on Serum Cholesterol and Lipoproteins

By DENHAM HARMAN, M.D., PH.D.

OXIDATION of constituents of serum lipoproteins to form compounds of higher molecular weight has been postulated as one of the initiating steps in the pathogenesis of atherosclerosis.[1] Studies of storage of isolated lipoproteins have shown that oxidative reactions occur which result in a shift of the low-density lipoprotein pattern toward lower S_f^0 values.[2] Hence, if the postulated in vivo oxidation of lipoproteins plays a significant role in determining the observed lipoprotein levels, then increasing the serum concentration of an antioxidant might result in a shift in the pattern toward higher S_f^0 values. This possibility has been evaluated in a study of the effect of oral α-tocopherol acetate.*

Procedure and Results

Seventeen apparently normal working men in the age range of 23 to 45 years participated in the study.† Four blood samples were drawn from each person in the fasting state at intervals of 2 weeks; determination of total serum cholesterol and analysis of low-density lipoprotein were done on each sample. After the second blood sample was drawn, 9 participants were given 100 mg. of α-tocopherol acetate orally 3 times per day (7 a.m., 3 p.m., 11 p.m.) while the remaining 8 took 200 mg. 3 times per day; thus 2 blood samples were obtained before taking vitamin E, 1 sample after 2 weeks of the vitamin and the last blood sample after 4 weeks of therapy. The data are tabulated in table 1.

Plasma vitamin E levels for healthy adults usually fall within the range of 1.0 to 1.2 mg per cent.[3] Oral administration of 400 or 500 mg. of vitamin E per day for 12 days was shown to raise the plasma level by about 0.8 mg. per 100 ml.[4] Thus it would be expected that the plasma vitamin E levels of the participants in the present study were increased about 1.0 mg. per 100 ml. over their normal levels after 2 weeks on the vitamin to a value of about 2.0 mg. per 100 mg.; no measurements of the plasma vitamin levels after 4 weeks of therapy are available.

In 4 subjects given 400 mg. of α-tocopherol acetate per day for 3 days the following changes occurred in the μg. of α-tocopherol acetate per mg. low-density lipoprotein.[5]

Before	*After*
1.1	2.7
1.71	1.46
1.39	2.70
1.23	3.4

These data suggest that after several days of therapy individuals in the present work had serum low-density lipoprotein levels of vitamin E that were 2 to 3 times there normal values.

Discussion

The daily ingestion of 300 or 600 mg. of α-tocopherol acetate for 4 weeks had no significant effect on serum levels of total cholesterol or low-density lipoproteins. This result neither negates nor provides support for the hypothesis of in vivo oxidation of serum lipoprotein; the 2- to 3-fold increase in serum low-density lipoprotein content of vitamin E expected with the amounts of α-tocopherol employed[4] may not have been sufficient to cause

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†This study was conducted at the Donner Laboratory of Medical Physics, University of California, Berkeley, California. I wish to express my appreciation to the members of the laboratory who participated in this work and to Miss Ardra Cornelius for the lipoprotein determinations.

Table 1

Effect of Oral Vitamin E on Serum Cholesterol and Lipoprotein Levels

Participant	Sample no.	Cholesterol mg. %	S_f^o 0-12	S_f^o 12-20	S_f^o 20-100	S_f^o 100-400	Atherogenic index
A. 100 mg. α-tocopherol acetate 3 times per day							
1.	1	271	454	77	114	56	89
	2	252	415	61	126	49	83
	3	260	372	83	104	37	76
	4	269	447	68	94	7	74
2.	1	252	440	66	28	0	60
	2	226	443	55	12	0	56
	3	211	396	28	29	10	51
	4	254	455	80	83	11	76
3.	1	241	334	51	56	14	55
	2	176	273	28	51	11	43
	3	166	251	4	0	0	26
	4	175	315	50	19	4	44
4.	1	253	350	104	73	18	69
	2	233	347	59	84	54	69
	3	267	420	85	49	18	69
	4	284	442	55	71	7	67
5.	1	191	322	48	51	14	52
	2	172	293	26	7	0	35
	3	175	327	15	29	10	42
	4	202	339	30	22	3	44
6.	1	290	484	86	45	7	73
	2	275	459	76	88	43	82
	3	280	475	76	105	69	91
	4	273	472	61	87	33	79
7.	1	245	409	74	98	30	76
	2	234	461	70	137	68	94
	3	238	398	37	143	106	90
	4	216	381	38	116	63	76
8.	1	192	266	52	100	22	57
	2	194	278	58	86	4	54
	3	187	307	45	105	40	64
	4	208	357	48	108	18	66
9.	1	175	221	64	81	11	49
	2	168	246	34	75	14	46
	3	182	300	35	41	14	46
	4	177	259	52	83	53	59

an appreciable inhibition of the rate of the postulated oxidation or very little oxidation may occur in vivo in the low-density lipoproteins due to a short half-life in comparison to the rate of oxidation.

The fluctuations in serum cholesterol and lipoprotein levels in the participants under conditions of normal living are worthy of note; the difference between the highest and lowest of the 4 serum cholesterol values for each individual varied from 7 to 84 mg. per cent, with an average for the group of 35 mg. per cent, whereas the corresponding figures for the Atherogenic Index are 2 to 48 and 19 respectively. These fluctuations should be taken into account in assessing the significance of reported single determinations of serum cholesterol and lipoprotein levels.

Summary

Vitamin E had no significant effect on serum levels of cholesterol or lipoproteins when taken orally by normal working individuals at the level of 300 or 600 mg. per day for a period of 4 weeks.

Summario in Interlingua

Vitamina E habeva nulle significative effecto super le nivellos seral de cholesterol o de lipoproteinas quando prendite per normal subjectos sub conditiones normal in doses de 300 a 600 mg per die durante un periodo de 4 septimanas.

Table 1—(Continued)

Effect of Oral Vitamin E on Serum Cholesterol and Lipoprotein Levels

Participant	Sample no.	Cholesterol mg. %	S_f^0 0-12	S_f^0 12-20	S_f^0 20-100	S_f^0 100-400	Atherogenic index
B. 200 mg. α-tocopherol acetate 3 times per day							
10.	1	223	333	22	54	14	49
	2	207	383	16	11	24	47
	3	224	351	26	33	14	48
	4	225	406	35	62	14	60
11.	1	273	398	68	227	320	147
	2	362	430	101	266	307	161
	3	295	449	98	287	256	157
	4	311	540	96	159	82	113
12.	1	198	313	52	77	29	59
	2	203	272	41	71	21	50
	3	147	260	27	111	72	63
	4	185	302	25	101	61	63
13	1	216	325	28	132	143	86
	2	241	405	48	75	36	68
	3	224	351	44	60	33	59
	4	215	352	37	63	29	58
14.	1	237	416	35	66	58	69
	2	232	382	37	90	106	79
	3	225	429	41	92	51	75
	4	237	371	34	55	50	61
15.	1	211	381	38	37	10	53
	2	182	282	15	24	4	36
	3	194	417	36	54	11	59
	4	201	349	29	69	40	59
16.	1	209	424	42	11	5	53
	2	235	393	30	7	0	46
	3	237	429	42	15	0	53
	4	252	477	39	42	11	64
17.	1	179	366	22	53	22	54
	2	169	299	4	63	43	49
	3	208	341	18	77	58	61
	4	206	416	22	61	32	62

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CLINICAL PROGRESS

Respiration and Circulation in Patients with Portal Cirrhosis of the Liver

By H. O. HEINEMANN, M.D.

IT IS generally known that cirrhosis of the liver may be accompanied by marked changes in the hepatic and splanchnic vasculature, which in turn lead to reduced hepatic blood flow, increased portal venous pressure, and the development of collateral vessels permitting bypass of the diseased liver.[1-7] Less well known is the fact that cirrhosis of the liver may also be associated with changes in the respiratory pattern, the pulmonary vasculature, and the systemic circulation.[8-10] Information on this subject is at present incomplete. It may even seem questionable that impairment of the function of a single organ can lead to such a varied pathologic pattern. This review attempts to fulfill a dual purpose: first, to draw attention to the above-mentioned, less well known complications of cirrhosis of the liver, and, secondly, to present a more unified concept of the respiration and circulation in patients with this disease.

Patients with cirrhosis of the liver may hyperventilate at rest in the absence of reduced hemoglobin content of the blood and without apparent increase in oxygen consumption. This leads to the development of mild respiratory alkalosis.[10] To explain the hyperventilation in the face of reduced carbon dioxide tension and normal, or slightly elevated, pH of the arterial blood, the assumption is often made that the respiratory center is stimulated by ammonia, because the blood level of this metabolite is frequently elevated in patients with liver disease.[11] Poor correlation between the ammonia content of arterial blood and the minute ventilation casts some doubt on the significance of ammonia as a respiratory stimulus and leaves this problem open for further investigation.[9] Another stimulus that must be considered to explain the hyperventilation is the low oxygen tension of arterial blood, not infrequently observed in patients with cirrhosis of the liver. Determination of the partial pressure of oxygen in arterial blood reveals tensions, however, which are not of the order of magnitude commonly assumed to be necessary to increase ventilation,[9, 12] and the mechanism maintaining hyperventilation in the absence of adequate physiologic stimuli (pCO_2, pH, and pO_2) remains, at present unsatisfactorily explained.

The above-mentioned low arterial oxygen tension, observed in some patients with cirrhosis of the liver, leads to an increased gradient in the partial pressure of oxygen between the blood and alveolar air.[13] This gradient is further accentuated by the high alveolar oxygen tension caused by hyperventilation. The low arterial oxygen tension in cirrhosis of the liver might be due to hypoventilation of well-perfused lung tissue, because of elevation of the diaphragm secondary to ascites, or these patients may have intrinsic lung disease with reduced diffusing capacity for oxygen. Pulmonary function remains within normal limits and unsaturation of arterial blood persists, however, irrespective of the presence or absence of ascites,[9] and paracentesis has no apparent effect on ventila-

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ion.[14] It is also conceivable that changes in the hemoglobin molecule, leading to a shift in the oxygen dissociation curve, may be responsible for the hypoxemia in liver disease.[15, 16] Such a mechanism can similarly be excluded, however, because blood of hypoxemic patients becomes fully saturated by equilibration in vitro with gas mixtures containing oxygen at tensions similar to the ones observed in vivo.[9]

These considerations leave shunting of venous blood into the systemic circulation as a third possibility to explain the hypoxemia of liver disease. The presence of such venous-to-arterial shunts is made likely by the fact that administration of 100 per cent oxygen does not abolish either the increased gradient for oxygen tension between alveolar air and arterial blood, nor the hypoxemia in patients with marked unsaturation.[8, 17] In adults with portal cirrhosis, in contrast to patients with so-called juvenile cirrhosis,* these shunts are apparently not located between the pulmonary arteries and pulmonary veins.[18, 19] Abnormal vascular channels, which could account for extrapulmonary shunting of venous blood into the systemic circulation, have been documented by Calabresi and Abelman,[20] who demonstrated communications between the portal vascular bed and the pulmonary veins via periesophageal and mediastinal veins. The volume of portal venous blood entering the systemic circulation per unit of time must depend on the available pressure gradient between the portal and pulmonary veins and may, therefore, vary considerably during the respiratory cycle because of the unusual location across the diaphragm.†

Unpublished observations indicate that cirrhosis of the liver may in some instances be associated with changes in the pulmonary arteries (vasculitis?) and an elevated pulmonary artery pressure. The underlying mechanism is at present not understood. But the question arises whether there is a relationship between the pulmonary hypertension and the fact that metabolites, originating from the gastrointestinal tract, have direct access to the pulmonary arteries via acquired or surgically induced anastomoses of portal vein to vena cava. It is tempting to compare this situation with the pulmonary hypertension in patients with the carcinoid syndrome, where serotonin escapes hepatic inactivation because of overproduction or metastases beyond the liver and then affects the pulmonary vessels. At present, however, there is no evidence to suggest that the changes in the pulmonary arteries, occasionally observed in patients with cirrhosis of the liver, are due to a specific metabolite such as serotonin.*

Patients with cirrhosis of the liver may have unexplained cardiac hypertrophy. Lunseth, Olmstead, and Abboud[23] reported such cardiomegaly in 12 out of 108 autopsies on patients with portal cirrhosis, an incidence of 11 per cent. Coronary artery disease and hypertension are generally considered to be less common in these patients.[24] To account for this abnormality, one has therefore to consider other mechanisms. One possibility would be that portal cirrhosis is associated with a specific type of myocardial disease. Such a mechanism is not unlikely because microscopic examination of the myocardium in the patients studied by Lunseth, Olmstead, and Abboud[23] and others[25] revealed an unusual type of diffuse fibrosis, often only in portions of a single muscle fiber.

Predominant right ventricular hypertrophy is another characteristic feature of the cardiomegaly in patients with cirrhosis of the liver. This may be due to the occasionally observed increased pulmonary artery pressure. It is also known that patients with cirrhosis of the liver may have a high cardiac output at rest, irrespective of the presence or absence of collateral circulation, portocaval shunt, anemia,

Rydell and Hoffbauer[18] observed arteriovenous anastomoses between the pulmonary artery and the pulmonary vein in a patient with juvenile cirrhosis.

†The so-called shunt equation cannot be applied to calculate the volume of blood flowing through these vascular communications because the oxygen content of portal blood is not readily measurable.[21]

*The serotonin content in blood of patients with cirrhosis of the liver is reported to be lower than in normal subjects.[22]

or nutritional deficiencies.[8, 26–28] Such persistent elevation of the cardiac output could account for cardiac hypertrophy. The increase in cardiac output is not associated with increased oxygen consumption and is therefore different from the circulatory pattern observed in the so-called hypermetabolic state. The rise in cardiac output is similar to the change noted in patients with arteriovenous fistulae[29, 30] and thiamine deficiency.[31] All these syndromes have in common a reduction of the peripheral resistance.

It is conceivable that cardiomegaly, perhaps in combination with degenerative changes in the myocardium, may lead to cardiac failure. No adequate information, however, is available on the incidence of such a complication in patients with cirrhosis of the liver. Dyspnea and cough, frequently noted in these patients, is usually ascribed to the elevated diaphragm because of ascites and the higher susceptibility to respiratory infections.[32] Peripheral edema is as frequent as ascites in these patients and may occur irrespective of the presence or absence of fluid in the abdomen.[32] Hydrothorax may develop, most commonly in association with ascites. Pulmonary infections or leakage of ascitic fluid into the pleural cavity is usually implicated as a cause. If heart failure, indeed, complicates cirrhosis of the liver, it may be difficult to detect because most symptoms can also be ascribed to the underlying disease. Measurement of venous pressure and the response to a cardiotonic regimen may be helpful in differentiating the cause of fluid retention. Furthermore, coincidence of cirrhosis of the liver and heart failure does not imply a causal relationship, because both conditions have a high incidence in the same age group. However, 2 well-documented cases of high output failure have been reported in the literature.[8, 18] Emphasis, therefore, on high output failure as a potential complication of cirrhosis of the liver seems justified and may lead to more frequent recognition.

The increased cardiac output in patients with cirrhosis of the liver is presumably due to decreased peripheral resistance and the resulting increased peripheral blood flow. These changes in the hemodynamic pattern are clinically discernible by the increased pulse pressure,[33] flushed palms, and capillary pulsations.[8, 34, 35] The mechanism responsible for the reduction in peripheral resistance is unknown. It has been postulated that either increased production or diminished inactivation of vasoactive substances is involved. Such a substance originating from the area drained by the splanchnic vessels and normally inactivated by the liver, could escape hepatic inactivation and gain access to the systemic circulation via collateral vessels. Increased levels of circulating estrogen[35] have also been implicated as a cause for both the development of palmar erythema (peripheral vasodilatation) and the appearance of arterial spiders.

Cirrhosis of the liver is occasionally accompanied by hypertrophic osteoarthropathy.[8, 34, 36] The cause of clubbing remains unknown, but it has been postulated that this abnormality is related to increased peripheral blood flow, increased cardiac output,[37] or shunting of venous blood into the systemic circulation, changes also observed in patients with portal cirrhosis of the liver. But hypertrophic osteoarthropathy is apparently more often observed in patients with biliary cirrhosis,[8] where such a hemodynamic pattern seems not to occur.

Patients with cirrhosis of the liver have frequently an enlarged total blood volume.[38–41] This is mainly due to an increase in the plasma fraction, the red cell mass being within normal limits. This leads to lowering of the hematocrit level, a fact that should be taken into consideration if the anemia of liver disease is to be evaluated. A normal hematocrit value in patients with cirrhosis of the liver, in the face of an elevated blood volume, represents a rise in red cell mass. It is conceivable that hypoxemia, if present, may stimulate red cell production and induce a relative or absolute polycythemia. Two such patients with cirrhosis of the liver and secondary polycythemia have been reported in the literature.[8, 18] The mechanism causing the rise in plasma volume is unknown. But a similar hypervolemia is observed in other conditions associated with

decreased peripheral resistance, such as arteriovenous fistulas,[42] thiamine deficiency,[31, 43] and pregnancy.[44] Reduction of the peripheral resistance, due to whatever mechanism, may conceivably initiate a cycle of events that ultimately leads to an increased plasma volume.[45, 46]

From the foregoing review, one can conclude that cirrhosis of the liver may be accompanied by marked changes in the respiratory pattern, pulmonary vasculature, and systemic circulation. Information about the incidence of these changes and their relationship to the stages of the disease and the type of cirrhosis is at present not available. Most observers have limited their studies to individual phenomena, such as the cardiac output, in selected patients. Rydell and Hoffbauer,[18] on the other hand, performed a careful study in a single patient with so-called juvenile cirrhosis and were able to define a disease entity characterized by hypoxemia, secondary polycythemia, high cardiac output, heart failure, and, apparently in contrast to adults with portal cirrhosis, multiple intrapulmonary arteriovenous fistulas. Comparable studies are not available in adults with cirrhosis of the liver. Such observations are necessary, however, before a similar disease entity can be confidently described for portal cirrhosis. As a working hypothesis for future studies, one can separate the changes observed in adults with portal cirrhosis into 3 different groups.

First, communications between the portal vascular bed and either the pulmonary veins or the venae cavae may (a) permit venous blood to enter the systemic circulation and cause hypoxemia or (b) may allow intestinal metabolites to escape hepatic inactivation and gain direct access to the systemic circulation.

Secondly, metabolites escaping hepatic inactivation may be responsible for the changes in the pulmonary vessels, pulmonary hypertension, reduced peripheral resistance, and hyperventilation.

Finally, reduction of the peripheral resistance leads to a rise in cardiac output and perhaps also the plasma volume. The increased cardiac output may eventually cause cardiac hypertrophy and heart failure, a complication difficult to recognize in older patients in whom heart disease may occur independently and fluid retention and dyspnea can be attributed to the underlying disease.

Acknowledgment

The author wishes to express his appreciation to Dr. A. P. Fishman for his suggestions and helpful criticism.

Addendum

Since this paper was submitted for publication, another well-documented example of arterial hypoxemia in cirrhosis of the liver has been described by Rodman and associates.[47]

Summario in Interlingua

Es generalmente cognoscite que cirrhosis del hepate pote esser accompaniate de marcate alterationes in le vasculatura hepatic e splanchnic e que isto, de su parte, resulta in un reduction del fluxo hepatic de sanguine, in un augmento del tension venose portal, e in le disveloppamento de vasos collateral que permitte le circuition del hepate morbide. Es minus ben cognoscite que cirrhosis del hepate pote etiam esser associate con alterationes del respiration, del vasculatura pulmonar, e del circulation major. Le presente articulo ha le duple objectivo de (1) signalar le supra-mentionate, minus ben cognoscite complicationes de cirrhosis del hepate e (2) presentar un plus unificate conception del respiration e del circulation in patientes con ille disordine.

In summation de su argumento e como base pro futur studios, le autor presenta le hypothese que le alterationes observate in patientes adulte con cirrhosis portal pote esser separate in tres differente gruppos.

1. Communicationes inter le vasculatura portal e, de un latere, le venas pulmonar o, del altere latere, le venas cave pote resultar in (a) le entrata de sanguine venose in le circulation major con le effecto de hypoxemia o (b) le non-inactivation de metabolitos intestinal per le hepate e le consequente transition directe de ille metabolitos a in le circulation major.

2. Metabolitos que escappa al inactivation per le hepate pote devenir responsabile pro alterationes in le vasos pulmonar, pro hypertension pulmonar, pro le reduction del resistentia peripheric, e pro hyperventilation.

3. Le reduction del resistentia peripheric resulta in un augmento del rendimento cardiac e forsan etiam del volumine de plasma. Le augmentate rendimento cardiac pote, in le curso del tempore, devenir le causa de hypertrophia cardiac e disfallimento del corde—un complication que es difficile a identificar in patientes de etates plus avantiate, proque in tales le

disveloppamento de morbo cardiac pote esser un occurrentia independente e le retention de liquido e le presentia de dyspnea pote esser interpretate como attribuibile al morbo subjacente.

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Medical Eponyms

By ROBERT W. BUCK, M.D.

The true worth of an experimenter consists in his pursuing not only what he seeks in his experiment, but also what he did not seek.—CLAUDE BERNARD. (Submitted by H. M. Marvin, M.D.)

Cigarette Smoking and Cardiovascular Diseases

REPORT BY THE AMERICAN HEART ASSOCIATION

IN 1956, the American Heart Association issued a statement on smoking and cardiovascular diseases. Among other things, this statement indicated that the available evidence at that time was not sufficient to justify conclusions concerning a cause and effect relationship between cigarette smoking and increased death rates from coronary heart disease (Appendix 1). Since then, sufficient additional knowledge has been accumulated to warrant a new report on cigarette smoking and its possible relationship to cardiovascular diseases. (See footnote and Appendices 2, 3, 4 and 5.)

Up to the present, a number of medical studies (Appendix 5) have been made, nearly all demonstrating a statistical association between heavy cigarette smoking and mortality (death) or morbidity (illness) from coronary heart disease. In these studies, death rates from coronary heart disease (heart attacks) in middle-aged men were found to be from 50 to 150 per cent higher among heavy cigarette smokers than among those who do not smoke. This statistical association does not prove that heavy cigarette smoking causes coronary heart disease, but the data strongly suggest tha heavy cigarette smoking may contribute to o accelerate the development of coronary hear disease or its complications.

Because coronary heart disease is the lead ing cause of death and a major cause of dis ability in the American population, the Amer ican Heart Association believes that thes studies concerning cigarette smoking and cor onary heart disease should be called to th attention of the medical profession, allie health professions, health educators, and th general public. The association recognizes th need for more knowledge and will continue t encourage systematic biological and medica research in order to determine whether a causal relationship exists between cigarett smoking and coronary heart disease and also to determine the effects of smoking in relation to strokes and other important aspects of cardiovascular diseases.

Ad Hoc Committee on Smoking and Cardiovascular Disease:

L. N. KATZ, M.D., *Chairman,* Chicago, Ill.

E. V. ALLEN, M.D., Rochester, Minn.

M. CHERKASKY, M.D., New York, N. Y.

F. W. DAVIS, M.D., Baltimore, Md.

T. R. DAWBER, M.D., Framingham, Mass.

Smoking and health: Joint report of the study group on smoking and health. Science 125: 1129, 1957.

APPENDIX 1

Statement on Smoking Issued in 1956 by American Heart Association

The text of the report of the Committee on Smoking and Cardiovascular Disease given publicity in 1956 follows:

1. There is evidence supported by clinical observations in a large number of cases, that tobacco smoking is harmful in certain diseases of the peripheral blood vessels of the arms and legs. This harmful effect is demonstrated most clearly in the condition known as thrombo-angiitis obliterans (Buerger's disease). It is known that this disease will usually continue to progress if the patient continues to smoke, and that it will usually become stationary, or even improve, if he stops smoking. If smoking is resumed, the disease will usually become active again.

2. It is recognized that a small percentage of persons with known disease of the coronary arteries will develop symptoms and will display signs detectable by laboratory tests when they smoke. Such people may be harmed by smoking.

3. The Committee believes that the available evidence is not sufficient to define the effect of tobacco smoking upon the coronary arteries or upon the heart itself, except in the small group mentioned above who already have coronary artery disease. It is believed that if smoking plays any part in the causation of heart disease, it is only one of many factors.

4. It is the belief of the Committee that much greater knowledge is needed before any

conclusions can be drawn concerning relationships between smoking and increased death rates from coronary heart disease. The acquisition of such knowledge may well require the use of technics and research methods that have not hitherto been applied to this problem.

5. Consequently, it is recommended that the continuing interest of the American Heart Association be implemented by the appointment of a technical committee representing a wide range of research experience to suggest the lines of investigation that may be most productive.

APPENDIX 2

Summary of Recent Reports on the Biologic Effects of Cigarette Smoking on the Cardiovascular System

By GRACE M. ROTH, PH.D., ALBUQUERQUE, N. MEX.

Effects of Smoking on the Peripheral Vascular System

Again the question has arisen of the possible allergic activity of tobacco as a cause of certain peripheral vascular diseases. Further work by Fontana and co-workers demonstrated that 33 per cent of the smokers with positive skin reactions to tobacco extracts gave a personal history of allergic manifestations and peripheral vascular symptoms, as compared with 10 per cent of the smokers who did not react to the skin tests. On smoking, 23 per cent of smokers with positive skin tests to tobacco had changes in the peripheral circulation indicated by a fall in skin temperatures of the extremities, as compared with the smokers with negative skin tests, 4 per cent of whom had changes in the skin temperatures.

Previously it had been shown in the rabbit that the constrictor action of nicotine was unaffected by degeneration of all sympathetic fibers to the ear after removal of the stellate and superior cervical ganglia. In contrast, Roth and Shick found no vasoconstriction in the lower extremities of patients during smoking if bilateral lumbar sympathetic ganglionectomy of the first and second lumbar ganglia was complete, but they found a considerable fall in the skin temperatures of the fingers. Thus, after bilateral lumbar sympathetic ganglionectomy, the remainder of the sympathetic nervous system seemed to function in a more than adequate manner.

In 1957, Nordenstam and Adams-Ray described the presence of chromaffin tissue in human skin. Lader, Burn and co-workers studied the effects of nicotine on the perfused vessels of rabbits' ears treated with reserpine and found that nicotine no longer produced vasoconstriction because of the depletion of norepinephrine and epinephrine. Therefore, they suggested that peripheral vascular disease could be explained by a hypersensitivity to the action of nicotine in releasing catecholamines from chromaffin tissue located near the blood vessels of the skin.

The controversy in regard to the elevation of the fasting blood sugar by smoking has continued over a period of years. Rehder and Roth found that when 24 normal subjects under basal conditions smoked two thirds of 2 cigarettes, there was no appreciable rise in the levels of the fasting blood sugar and the epinephrine-like substances in the venous blood. However, the blood pressure and pulse rate were significantly raised and the skin temperatures of the fingers and toes were decreased. Thus, this amount of smoking had an effect on the circulation but no significant effect on the fasting blood sugar.

Effects of Tobacco on the Heart

Most investigators agree that the effects of smoking tobacco or of the intravenous injection of nicotine on the heart are an increase in the pulse rate and elevation of the arterial blood pressure and some flattening of the T waves in the electrocardiograph. Two conflicting opinions have developed as to the cause of these effects: (1) that the changes are due solely to the increased work of the heart, or (2) that the changes are due to spasm or constriction of the coronary arteries.

Work on Animals

In 1950 and 1959, Rinzler and co-workers demonstrated that blood flow in the perfused coronary arteries of normal rabbits was increased after the injection of nicotine. On the other hand, when the rabbits had been made atherosclerotic by a high cholesterol diet, nicotine caused a decline in flow through the perfused coronary vessels.

Likewise, West, Guzman and Bellet, working on dogs, catheterized the circumflex and anterior descending branch of the left coronary artery via 1 carotid artery and cannulated the coronary sinus via 1 external jugular vein. They concluded that there was no evidence of coronary constriction following administration of nicotine and that the explanation for the effect was that nicotine influenced the parasympathetic and sympathetic ganglia and chemoreceptors in the heart.

Kien, Lasker and Sherrod determined the effect of cigarette smoke on the open-chest, anesthetized dog by measuring blood pressure, cardiac output,

coronary blood flow, cardiac oxygen consumption, cardiac work and the electrocardiographic effects. A lack of correlation was observed between the onset of the electrocardiographic effects and the changes in cardiac work. Coronary blood flow increased and appeared to follow the changes in blood pressure and cardiac output. The authors suggested that the electrocardiographic disturbances subsequent to the inhalation of cigarette smoke were not due entirely to increased cardiac work or to coronary vasoconstriction, but rather to decreased oxygen consumption. They felt that this latter factor was of prime importance in the precipitation of "tobacco angina pectoris."

In 1959, Armen and Cohen studied the effects of forced inhalation of tobacco smoke on rabbits previously sensitized to tobacco proteins. They concluded that the cardiovascular effects demonstrated by abnormalities of the electrocardiogram were due to anoxia and not to immunologic effects.

A different concept has been introduced by Burn and Rand. They demonstrated that the stimulant action of nicotine on the isolated atria of the heart of rabbits was due to a release of norepinephrine and epinephrine from the stores within the heart. Such stores of these amines could be depleted by giving reserpine; subsequently nicotine did not stimulate the depleted atria. The stores of norepinephrine and epinephrine in the normal heart exert some effect and accelerate the spontaneous rate of the heart. This was shown when the mean rate of the atria in the control animals was 142 beats per minute, while the mean rate of the atria treated with reserpine was 112 beats per minute. From this work, they concluded that smoking can liberate norepinephrine and epinephrine from the stores within the heart, thereby producing acceleration, and may cause or exaggerate ventricular arrhythmias.

Work on Humans

The general consensus is that smoking tests carried out by means of the ballistocardiograph were more discriminating than any other objective method in separating patients with coronary disease from normal controls. Thomas, Bateman, Lindberg, and Bornhold studied the ballistocardiographic effects of smoking on 113 healthy medical students, 103 men and 10 women, who were 21 to 35 years of age. In both smokers and nonsmokers, the systolic and diastolic pressure, pulse pressure, heart rate, stroke volume, cardiac output, and cardiac index showed statistically significant changes on smoking 1 cigarette.

There was quite good correlation between the pattern of response to smoking and the family history regarding hypertension or coronary disease. As a group, subjects with parental hypertension showed a significantly greater rise in cardiac output than expected, while stroke volume and cardiac output were significantly smaller than anticipated among the offspring of parents with coronary disease. No such relationship between familial hypertension and hyperreactivity to smoking had previously been described. The studies indicated that hyperreactivity to smoking is related to hyperreactivity to the cold pressor test and that hypertensive patients react more strongly to smoking than do normotensive subjects; this is in harmony with the hypothesis that hyperreactivity appears particularly frequently in individuals who are the offspring of hypertensive parents and may be a precursor of hypertension in a given individual.

From the above facts, it appears that change in cardiac output after smoking is likely to be the most valuable part of the ballistocardiographic smoking test in screening possible candidates for hypertension or coronary disease.

Again in 1959, Thomas and Murphy, to test the reproducibility of the above ballistocardiographic smoking tests, gave 32 men 4 tests each, 2 before breakfast and 2 before lunch, and 6 subjects 8 tests each, under circumstances kept as standard as possible in every way.

From these findings, it appears that the ballistocardiographic smoking test, in which blood pressure, heart rate, stroke volume, and cardiac output are measured, gives results which are sufficiently reproducible for use as a screening test to classify young adults according to their patterns of circulatory reactivity. The results were materially unchanged by attempts to standardize further the test conditions, except that on the average the response was more marked in the fasting state.

The first studies using direct catheterization of the coronary sinus and a needle in the femoral artery were carried out on 30 human beings by Bargeron and co-workers. They found that smoking a cigarette caused a significant rise in coronary blood flow and heart rate, a significant decline in coronary vascular resistance and myocardial extraction of oxygen and glucose.

The evidence that cigarette smoking does not reduce coronary flow in normal individuals is in agreement with observations that electrocardiographic or ballistocardiographic changes are absent in individuals without coronary disease. However, from electrocardiographic or ballistocardiographic observations on patients with coronary heart disease, one may suggest that these individuals respond to smoking by a decrease in coronary blood flow and an increase in coronary vascular resistance. This assumption is borne out by Rinzler, who found that nicotine increased the coronary flow through a perfused normal rabbit's heart, but when the animal had been made atherosclerotic by a high

cholesterol diet, nicotine resulted in a decline in flow through the perfused coronary vessels.

Although extensive work has been carried out to determine the cause of the changes in the heart during smoking, the controversy has not been settled. However, with new and more critical instrumentation, the answer may be forthcoming.

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APPENDIX 3

Summary of Reports Pertaining to Cigarette Smoking and the Cardiovascular System: Clinical Data 1956-60

By FRANK W. DAVIS, M.D., BALTIMORE, MD.

A review of the English literature of the years 1956-60, inclusive, produced little of primary clinical nature in which the effects of smoking (or nicotine) on the cardiovascular system were considered. Several reports of great interest from the epidemiologic viewpoint were published, but these undoubtedly will be summarized by Dr. Dawber. The much discussed New England, California, and English statistical studies were enlarged during this period.

The most comprehensive report, dealing with most of the known physiologic actions of smoking and touching only briefly on the clinical features, is the excellent review paper of Roth and Shick.[1] This doubtless will be included in Dr. Roth's summary. Of review nature, but in a briefer form, is the paper by Burn,[2] in which he outlines his concept of the physiologic and pharmacologic effects of nicotine on the heart. He continues to express the view that smoking triggers the release of a sufficient quantity of vasopressin to elicit coronary vasoconstriction, with the alternative explanation of nicotine effect being direct action on chromaffin tissue and stimulation of epinephrine or norepinephrine release. He suggests abstinence from smoking in patients with clinical coronary disease.

In a rather extensive clinical review, oriented from the allergic point of view, Harkavy[3] summarizes the investigations of himself and others, including an evaluation of skin testing of smokers and nonsmokers with and without various vascular disorders, to various tobacco extracts. Approximately 9 per cent of nonsmokers react positively to these extracts, 41 per cent of smokers showing a positive skin test. In patients with thrombo-

angiitis obliterans, the incidence of positive tests is 78 per cent. Experimentally, rats can be sensitized to tobacco extracts, and in 33 per cent of such rats, gangrene of the extremities appeared. He concluded from the skin sensitivity studies and from general clinical observation that not only thromboangiitis obliterans, but some arrhythmias and angina, can be related to tobacco allergy.

Thomas and her co-workers have published 3 papers in this period which have potential clinical implication. In the first of these,[4] she observed the changes in blood pressure, pulse, and ballistocardiographically determined cardiac output and stroke volume in healthy medical students. There was considerable variability, but each individual seemed to show consistent changes in each parameter studied. Those with a family history of hypertension were hyperreactors (increased output) and those with family histories of coronary disease generally showed a subnormal response. In a subsequent report,[5] these effects were shown to be fairly reproducible when studied in the same subjects under various conditions and over a several year period. A third report[6] compared these circulatory reactions to smoking with the response to the cold pressor test. Interestingly, these stimuli did not correlate well, and "independent information seems to be gained from each test." The changes resulting from either seemed to be a continuous variable, without clear separation of her subjects into groups, and without definite prognostic information to be gained.

The last group of papers of clinical nature is related to observations on the effect of smoking on the ballistocardiogram. Strober published 2 papers[7, 8] in which a presumably normal Air Force population was studied with regard to ballistocardiographic pattern change after smoking. He found practically no evidence of ballistocardiographic deterioration in his young males but a rapidly increasing incidence with increasing age, so that 72.7 per cent of those in the 45 to 51 year group responded positively. Obesity likewise seemed to increase the incidence of positive reactions. He concludes that this test may detect asymptomatic coronary artery disease.

Our group published further observations on the ballistocardiograph cigarette test as a diagnostic method in coronary heart disease.[9] This represents an extension of previously reported studies in which it was shown that patients with ischemic heart disease react with ballistocardiographic deterioration after smoking much more frequently than do the apparently normal subjects. Filtered or "denicotinized" cigarettes failed to prevent this deterioration. This "test" is presented more as a challenge to the clinical investigator than as a routine clinical procedure.

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Appendix 4

Summary of Recent Literature Regarding Cigarette Smoking and Coronary Heart Disease

By Thomas R. Dawber, M.D., Framingham, Mass.

In reviewing the problem of the relationship of tobacco smoking to coronary heart disease, Sigler[1] stated: "It has been well established that tobacco smoke induces certain immediate effects on the cardiovascular system. These may consist of an acceleration of the heart rate, a rise in blood pressure, a decrease in the temperature of the fingers and toes, a diminution of the blood

flow to the extremities, and minor electrocardiovascular changes, such as diminished amplitude of the T waves." After considering the physiologic effects of tobacco on the circulatory system, he concluded that "although the immediate manifestations are expressions of physiologic disturbances, it is conceivable that accumulative effects of tobacco intoxication over years may result also in structural changes. To prove or disprove such an assumption, we must rely mainly on statistical studies of many cases observed over a period of years."

Studies which have been carried out in an endeavor to answer this question are of 3 general types:

Clinical Studies of Persons Who Have Developed Coronary Heart Disease

Representative of this group of studies is one by Sigler,[1] in which he examined the records of 1,520 cases of coronary heart disease and found that (1) the age at onset of clinical manifestations of coronary disease in this series occurred earlier in smokers than in nonsmokers; (2) the higher the degree of smoking the earlier was the onset of the clinical manifestations of the disease; and (3) the age at onset of the first attack of coronary occlusion also occurred earlier in the smokers than in nonsmokers in both males and females. He also found that the age at death was also younger in smokers than in nonsmokers.

Mortality Data from Large Populations Including Smokers and Nonsmokers

Although studies of mortality data are open to the objection that causes of death as attested to by death certificates and examining physicians are not completely reliable, there is no reason to believe that there is a different degree of accuracy in deaths of smokers as compared to nonsmokers. Comparability of the 2 groups in the *same* population is therefore a valid exercise.

The most recent and extensive study of this type is that of Dorn,[2] who has been following carefully 198,926 Veterans Administration policy holders in whom smoking data and cause of death information could be obtained. According to Dorn, the death rate from coronary heart disease was 63 per cent higher for cigarette smokers than for nonsmokers. This increase did not hold true for pipe and cigar smokers who had a death rate "not appreciably higher than nonsmokers."

Dorn's report is in agreement with the report of Hammond and Horn,[3] who state that "death rates from coronary heart disease were far higher among men with a history of regular cigarette smoking than among men who never smoked." The death rate was 70 per cent higher in cigarette smokers than a comparable group of nonsmokers.

On the other hand, Haag and Hanmer,[4] in a study of workers in the American Tobacco Company, found that the mortality rates from cardiovascular disease were lower in these tobacco workers, although the number of tobacco smokers and the average amounts smoked was higher than in the general population. This study, however, did not make an internal comparison of smokers and nonsmokers, but compared the group of workers in the American Tobacco Company with the general population. The extent to which generalizations can be drawn from comparison of these 2 groups is unknown since they may differ in a number of characteristics.

Prospective Studies Involving Small Population Groups in Whom Morbidity Data, as Well as Mortality Data, Are Available

In these studies, there is more thorough knowledge of the characteristics of the population studied and its comparability to the general population than in the case of mortality studies; also, the reliability of the diagnosis of coronary heart disease is far higher. Nevertheless, due to the lengthy follow-up necessary to obtain sufficient cases for study, many of the reports are yet inconclusive. For example: Doyle et al.[5] have stated that "no clear relation between the incidence of ischemic heart disease and the consumption of tobacco in any form has been demonstrated. The numbers involved, however, are too small to permit a reliable estimate." This conclusion was based on a study of 1,913 men followed for approximately 4 years. They stated: "There appears to be no trend toward an increasing incidence from the light to the heavy smoking category." They concluded, however, that a further follow-up is needed to establish any relationship. Similarly, Dawber et al.[6] have reported: "Study of the relation of smoking to the development of all new cases of coronary heart disease continues to show a lack of association. . . ." "When, however, a separate analysis is made of those cases manifesting more severe degrees of coronary heart disease, excluding those with angina pectoris alone, an association of risk with cigarette smoking seems to emerge, the risk rising with the number of cigarettes smoked per day." When they considered the mortality experience, they concluded: "Findings are consistent with those involving larger populations but based on too few cases of coronary heart disease to indicate a definite association with smoking."

Buechley et al.,[7] however, after reviewing several studies and adding their own study of 3,994 longshoremen, concluded that "the difference in death rates between nonsmokers and smokers shows a strong and consistent relationship between cigarette smoking and coronary heart disease mortality, at least in men 40 to 70 years of age."

Conclusion

It, therefore, seems possible that when examination of mortality data has been the basis of the study, conclusions have been reached which clearly relate increased cigarette smoking to an increase in death rates from coronary heart disease. In those studies in which morbidity data have been used (i.e., new cases of disease in the living), it has not been possible clearly to link increased cigarette smoking to the occurrence of coronary heart disease. However, such studies have not been carried on for a sufficiently long period of time to demonstrate definitely what the relationship may be. Such studies should ultimately be able better to define the relationship.

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APPENDIX 5

References

The article by Buechley, R. W., Drake, R. M., and Breslow, L., entitled: "Relationship of amount of cigarette smoking to coronary heart disease mortality rates in men" (Circulation 18: 1085, 1958), summarizes the studies listed below which support the statistical association between cigarette smoking and mortality or morbidity from cardiovascular diseases:

HAMMOND, E. C., AND HORN, D.: Smoking and death rates—report on forty-four months of follow-up of 187,783 men. I. Total mortality (pp. 1159-1172). II. Death rates by cause (pp. 1294-1308). J.A.M.A. 166: 1159 and 1294, 1958.

DOLL, R., AND HILL, A. B.: Lung cancer and other causes of death in relation to smoking: Second report on the mortality of British doctors. Brit. Med. J. no. 5001: 1071, 1956.

MILLS, C. A., AND PORTER, M. M.: Tobacco smoking and automobile-driving stress in relation to deaths from cardiac and vascular causes. Am. J. Med. Sc. 234: 35, 1957.

HEGGLIN, R., AND KEISER, G.: Über Rauchen und Coronarerkrankungen. Schweiz. med. Wchnschr. 85: 53, 1955.

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GERTLER, M. M., WHITE, P. D., AND OTHERS,: Coronary Heart Disease in Young Adults: A Multidisciplinary Study. Cambridge, Mass., Published for Commonwealth Fund by Harvard University Press, 1954.

MILLS, C. A.: Tobacco smoking: Some hints of its biologic hazard. Ohio Med. J. 46: 1165, 1950.

The following studies, also supporting the statistical association between cigarette smoking and mortality or morbidity from cardiovascular diseases, have been reported since the article by Buechley et al. was published:

DORN, H. F.: Tobacco consumption and mortality from cancer and other diseases. Pub. Health Rep. 74: 581, 1959.

ZUKEL, W. J., ET AL.: *In* A.P.H.A. Conference Report: Smokers double nonsmokers in heart disease. Pub. Health Rep. 74: 241, 1959.

The following studies question the methods used in studying the statistical association between cigarette smoking and mortality or morbidity from cardiovascular diseases:

DORN, H. F.: Mortality of smokers and nonsmokers; with discussion by Hopkins, C. E., Hammond, E. C., Hockett, R. C., and Meier, P. *In* Proceedings of the Social Statistics Section of the American Statistical Association 1958 Annual Meeting (Chicago), pp. 34-71. Published by the American Statistical Association, Washington, D.C.

BERKSON, J.: Smoking and lung cancer: Some observations on two recent reports. J. Am. Stat. Assn. 53: 28, 1958.

ABSTRACTS

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SURGERY AND CARDIOVASCULAR DISEASE

Kraus, W. L., Schlant, R. C., Moore, C. B., Dock, D. S., Woodward, E. Jr., Haynes, F. W., and Dexter, L.: The Hemodynamic Results of Surgery for Aortic Stenosis. Am. Heart J. 58: 174 (Aug.), 1959.

Hemodynamic data obtained from left heart catheterization of 19 patients with severe aortic stenosis before and after transaortic valvuloplasty are presented in detail. With pure aortic stenosis the cardiac index was normal, but was reduced with concomitant aortic regurgitation and mitral or coronary heart disease. Progressively severe aortic stenosis often became associated with a reduced cardiac output and a small mean pressure difference across the aortic valve. In 11 patients a small, but significant, increase in the calculated aortic valve area was found postoperatively. In these patients there was an associated marked fall of left ventricular systolic pressure, transvalvular pressure difference and left ventricular work while cardiac output remained unchanged. In 8 patients no change was found in the valve area postoperatively. In these patients the left ventricular systolic pressure and transvalvular pressure difference was also decreased, but this was found to be the result of reduced cardiac output. Six of the 8 operative failures occurred in 7 patients with clinically "insignificant" aortic regurgitation as the only complicating lesion. Associated mitral stenosis, mitral regurgitation, or coronary disease did not preclude successful surgery for aortic stenosis. In regard to the indications for aortic valve surgery it is concluded that surgery should be withheld until the development of angina, syncope, or heart failure, the onset of which indicates a poor prognosis with a life span of about 2 years. In this clinic the surgical risk employing these indications was between 8 and 10 per cent.

SAGALL

Mahaim, C. A., van Nieuwenhuizen, C. L. C., D'Heer, H. A. H., and Slooff, F.: The Clinical Evolution of Shunt-Operations for Morbus Caeruleus: Results of 150 Operations, in a Long-Term Follow-Up. Am. Heart J. 58: 13 (July), 1959.

The long-term results of 141 patients who had 150 shunt operations for congenital cyanosis were evaluated. The more important of the preoperative factors adversely influencing the postoperative prognosis included: (1) those patients in which the malformation was not that of the classic tetralogy of Fallot; (2) those patients with electrocardiographic features of left or of extreme right ventricular hypertrophy; (3) those patients who were younger than 2.5 years or older than 17 years; (4) the patients in whom the cardiothoracic ratio by x-ray was 55 per cent or more; (5) the patients with hemoglobin levels less than 70 per cent or greater than 150 per cent; (6) the patients who were underweight by more than 10 per cent of the normal values; and (7) those patients in whom the signs of circulatory disturbances were accentuated at birth. When the above factors indicated a favorable preoperative prognosis, the operative mortality rate was only 4 per cent and the postoperative results were good to excellent in 90 per cent. In those patients

with an unfavorable preoperative prognosis the mortality rate was 10 times higher. The most successful results were obtained with the Potts operation. The majority of the unfavorable results developed during the first postoperative years. After 2 years or more a remarkable stabilization of the amelioration obtained from the operation (Potts, Blalock, and Brock procedures) was observed. In some, this amelioration was progressive, with the patients becoming better and not worse as time passed. In some patients, even after a period of several years, normal cardiac function was found by a special cardiac function test employed by the authors.

SAGALL

SURGERY AND CARDIOVASCULAR DISEASE

Orjebin, P., Heim de Balsac, R., and Dubost, Ch.: Extension of the Concept of the Inflammatory Post-commissurectomy Syndrome to Congenital Heart Disease after Surgical Treatment. Arch. mal. coeur 52: 931 (Aug.), 1959.

A 34-year-old woman was subjected to surgical closure of an atrial septal defect under extracorporeal circulation. One month after the intervention she showed fever and chest pain, with elevation of sedimentation rate and C-reactive proteins, subsiding after corticoid treatment; electrocardiogram and heart size remained unchanged. These were the typical symptoms of the "post-commissurotomy syndrome" except that pericardial or pleural effusion was absent. Similar changes were reported by authors after operative treatment of congenital heart disease. The "post-commissurotomy syndrome" accordingly is not specific for rheumatic heart disease and therefore cannot be ascribed to reactivation of a rheumatic process.

LEPESCHKIN

Stephen, C. R., Bourgeois-Gavardin, M., Dent, S., Brown, I. W., Jr., and Sealy, W. C.: Anesthetic Management in Open-heart Surgery: Electroencephalographic and Metabolic Findings in 81 Patients. Anesth. & Analg.; Current Researches. 38: 198 (May-June), 1959.

Eighty-one patients underwent open-heart surgery with a combination of low-flow extracorporeal circulation (DeWall oxygenator delivering flows of 15 to 50 ml. per minute per Kg.) and hypothermia (not under 30 C.). Nitrous oxide-oxygen anesthesia at extremely light planes was maintained with muscular relaxation being provided by succinylcholine drip. In order to counteract the acidosis usual in slow-flow perfusion, the patients were hyperventilated. The average blood pH was 7.50 during the procedure but sank to 7.31 in the recovery room. Twelve patients died following the operation, but all awakened immediately afterward and did not show central nervous system damage. A marked slowing of the encephalographic waves with increase of amplitude usually appeared at the beginning of low-flow perfusion but disappeared in 2 or 3 minutes. This pattern was the best indicator of cerebral hypoxia and was particularly useful in determining whether the cardiac function was adequate after termination of extracorporeal circulation.

LEPESCHKIN

UNCOMMON FORMS OF HEART DISEASE

Abrahams, D. G.: An Unusual Form of Heart-disease in West Africa. Lancet 2: 111 (Aug. 15), 1959.

Fifty-three Nigerian patients are described who suffered a condition resembling rheumatic heart disease with an unusual distribution of lesions. The patients, mainly children and young adults complained of cough, breathlessness and chest pain; about half presented in frank cardiac failure. The clinical picture was dominated by signs of mitral incompetence and pulmonary hypertension. There was never evidence of mitral stenosis or aortic valve involvement. In 16 patients, there were, in addition, signs of acute carditis. Radiologically, the heart was always enlarged characteristically on the right; the electrocardiogram also reflected right ventricular dominance and atrial enlargement. Cardiac catheterization confirmed the presence of pulmonary hypertension. In active carditis, antistreptolysin-O titers were elevated. Eleven cases were examined post mortem and showed left ventricular fibrosis affecting the endocardium and sometimes extending into the myocardium. The chordae of the mitral valve were commonly involved. Endocardial thrombosis was frequently present. The largest chamber was the right atrium in which aneurysmal dilatation produced gross incompetence of the tricuspid valve. Histologically, perivascular collections of cells were noted, indistinguishable from Aschoff nodes.

KURLAND

Bourne, G., Wedgwood, J.: Heart-disease and Influenza. Lancet 1: 1226 (June 13), 1959.

Fourteen cases of influenza, observed during the 1957 epidemic, were associated with cardiac disability. Atrial fibrillation was precipitated in 8 cases and atrial flutter in 1. In 4 of these the

electrocardiogram revealed signs of an underlying myocardial defect. Angina of effort was initiated in 2 of the 4 cases with coronary symptoms and the ischemic state was accentuated in 2. Influenza also increased the electrocardiographic abnormality in the latter 2 cases. In the remaining case, there was underlying myocardial abnormality of unknown etiology. The authors suggest that influenza appears to have a definite although transitory toxic effect upon the myocardium.

SHEPS

VALVULAR HEART DISEASE

Björk, V. O., and Malmstrom, G.: The Diastolic Pressure Gradient between the Left Atrium and the Left Ventricle in Cases of Mitral Stenosis. Am. Heart J. 58: 486 (Oct.), 1959.

Left atrial puncture was performed on 63 patients with mitral valvular disease. After measurement of the left atrial pressure, the catheter was passed through the mitral orifice into the left ventricle so that the diastolic pressure gradient between the 2 chambers could be calculated and a withdrawal curve from the left ventricle to the left atrium registered. The diagnosis in each case was verified by surgery. In 56 patients with mitral lesions—pure mitral stenosis in 35 and dominant mitral stenosis with a certain degree of regurgitation in 21—there was a positive diastolic pressure gradient between the left atrium and the left ventricle varying between 36 and 1 mm. Hg, with a mean value of 10.5 ± 0.9 mm. Hg. In the remaining 7 patients who had a mitral lesion in combination with other heart disease there was a positive diastolic pressure gradient between the left atrium and the ventricle, varying between 15 and 1 mm. Hg, with a mean value of 6.4 mm. Hg. In 14 patients the minute volume flow was measured during the determination of the pressure gradients. In this group there was a slight but probably not significant correlation between these 2 factors. No correlation was evident between the degree of pressure gradient and the size of the mitral orifice as determined at operation, the heart volume, or the patient's working capacity. It is concluded that a diastolic pressure gradient over the mitral orifice of at least 5 mm. Hg indicates the presence of a stenotic component in the mitral valves, but this pressure gradient does not help in separating pure mitral stenosis from mitral stenosis with regurgitation, nor does it help in evaluating the degree of such mitral regurgitation.

SAGALL

Bricaud, H., Cottin, D., Mathe, P., and Broustet, P.: Pulmonary Diffusion and Blood Flow in Mitral Disease. Arch. mal. coeur 52: 861 (Aug.), 1959.

Of 16 patients with mitral disease examined with the method of Riley and Cournand, 2 showed normal oxygen diffusion capacity but an increased pulmonary dead space or increased admixture of venous blood. One patient showed decreased oxygen diffusion capacity while other values were normal; in the remaining 13 patients all values were abnormal. These findings were explained by the thickening of alveolar and capillary walls, bronchiolar obstruction, and the presence of anastomoses between pulmonary arteries and pulmonary veins as well as between the latter and bronchial veins.

LEPESCHKIN

Connolly, J. E.: Left Ventricular Puncture in the Assessment of Aortic Stenosis. J.A.M.A. 171: 160 (Sept. 12), 1959.

Left heart catheterization with direct percutaneous puncture of the left ventricle is the safest, easiest, and most reliable method of measuring the pressure difference across the aortic valve. This procedure is a valuable tool in judging the severity of aortic stenosis for preoperative selection and postoperative evaluation of patients undergoing surgery. The procedure is usually combined with a direct brachial artery recording. It is performed at the same time as right heart catheterization and can be completed in but a few minutes. In the author's cases, 12 of the first 14 punctures resulted in successful entry into the left ventricle.

KITCHELL

Fish, R. G., Takaro, T., and Crymes, T.: Prognostic Considerations in Primary Isolated Insufficiency of the Pulmonic Valve. New England J. Med. 261: 739 (Oct. 8), 1959.

A 51-year-old man with isolated pulmonic valve insufficiency of at last 13 years' duration was followed for 26 months. During this time there was no evidence of deteriorization of the right ventricle. Other clinical and experimental observations are presented and discussed indicating that isolated pulmonic valve insufficiency is a well-tolerated lesion, unless complicated by pulmonary artery hypertension, and that by itself this lesion does not induce pulmonary hypertension.

SAGALL

Garten, J., and Kolmar, K.: Contribution to the Indirect Determination of Left Atrial Pressure in Mitral Stenosis. Ztschr. Kreislaufforsch. **48:** 454 (May), 1959.

In 50 patients with mitral stenosis the interval between the beginning of the aortic second sound and that of the mitral opening snap decreased with increase of the mean pulmonary capillary pressure, measured at the same time by cardiac catheterization. However, the scatter was quite considerable. When the interval was plotted against the difference between aortic pressure at the time of the second sound and the mean capillary pressure, all points fell nearly on a straight line. This aortic pressure was calculated from the blood pressure, determined by the auscultatory method, by adding to the diastolic pressure a fraction of the pulse pressure corresponding to the position of the incisura in the carotid pulse, optically registered with the phonocardiogram. The relaxation velocity of the left ventricle was 10.06 (8.5-11.5) mm. Hg per 0.01 second. This value was independent of the heart rate and the pulmonary capillary pressure, and could be used with greater accuracy than previous methods for estimation of left atrial pressure from the time of appearance of the mitral opening snap.

LEPESCHKIN

Julian, O. C., Lopez-Belio, M., Dye, W. S., Javid, H., Prec, O., El Issa, S., and Lima, A.: Simultaneous Repair of Mitral and Tricuspid Valves through Right Atrium and Interatrial Septum. Arch. Surg. **78:** 745 (May), 1959.

The results obtained by open operation for the correction of mitral valvular disease and concomitant tricuspid-annulus plication are presented. The 8 patients were in class 3 or 4 on the basis of cardiac status at the time of optimum medical management. The tricuspid insufficiency was considered to be secondary to mitral valvular disease. Repair was done under total cardiopulmonary bypass by way of the lateral wall of the right atrium and the interatrial septum. Plication of the annulus of the tricuspid valve was performed in each case. Either direct-vision commissurotomy or annulus plication was carried out on the mitral valve. One patient died because of uncontrollable ventricular fibrillation, which had its onset several minutes after restoration of cardiac action. The second patient had very high pulmonary vascular resistance and died shortly after restoration of rhythm to atrial fibrillation. Two late deaths occurred 40 and 70 days after surgery, because of wound infection. The remaining 4 patients (2 with stenosis and 2 with regurgitation) followed 2 to 12 months postoperatively, showed significant improvement in cardiac size and contour, exercise tolerance, and physical signs. On the basis of this experience, the authors suggest that unremitting tricuspid insufficiency is an additional indication for open-heart surgery of mitral stenosis. Moreover, when open repair is required for the mitral valve because of predominant regurgitation, concomitant tricuspid valve repair should be done. Every effort should be made to abolish secondary tricuspid insufficiency by medical means before surgery. Associated aortic stenosis may be dealt with at the same operation. Significant aortic regurgitation is a complicating factor in open valvular surgery for technical reasons. In addition, severe pulmonary vascular changes are a deterrrent to this form of mitral-tricuspid surgery.

SHEPS

Kahn, M., Bleifer, S. B., Grishman, A., and Donoso, E.: The Vectorcardiogram and Electrocardiogram before and after Valvulotomy for Pulmonic Stenosis. Am. Heart J. **58:** 327 (Sept.), 1959.

In 12 patients with severe pulmonic stenosis who were treated with valvulotomy the preoperative and postoperative electrocardiograms, and vectorcardiograms were correlated with hemodynamic data. No close correlation was found preoperatively between the level of right ventricular systolic pressure nor between the systolic gradient across the pulmonic valve and the electrocardiographic changes or the configuration of the QRSsŝ loop of the vectorcardiogram, but those patients with the highest right ventricular pressures tended to show inverted T waves in the precordial leads and rightward deviation of the electrical axis. Postoperatively, in any given case, serial electrocardiographic and vectorcardiographic changes did correlate with changes in the right ventricular load. In this series incomplete regression of the electrocardiographic and vectorcardiographic signs of right ventricular hypertrophy were found to indicate either an inadequate period of observation, incomplete correction of the stenotic lesion or the presence of other hemodynamically significant defects.

SAGALL

NEWS FROM THE AMERICAN HEART ASSOCIATION

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AHA Allocates $1,700,000 in Grants; Year's Awards to Exceed $9 Million

Grants-in-Aid totaling approximately $1,700,000 have been made to 216 investigators under the national research support program of the American Heart Association and its affiliates for the 1960-61 fiscal period.

Previously announced awards for 171 Fellows and Investigators, including seven continuing and two new Career Investigators supported by the Association on a life-time basis, bring to more than $3,600,000 the amount allocated for research by the AHA National Office, an all-time record for a single year. The sum represents approximately 59 per cent of income received by the National Office from public contributions to the 1959 Heart Fund appeal.

In addition, research awards by affiliated state and local Heart Associations will total an estimated $5,500,000, bringing to more than $9,000,000 the sums allocated by the Association for scientific research in the 1960-61 fiscal year.

Applications for 45 additional new grants-in-aid totaling approximately $350,000 were approved by the AHA Research Committee but could not be supported for lack of funds in the national research budget. These, and five fellowships previously approved without funds, have been referred to local Heart Associations for possible supplementary support over their regularly assigned sums for the national research program.

A complete list of recipients of new and continuing Grants-in-Aid appears at the end of this section.

Applications for Research Support Invited by Heart Association

Research investigators may now apply to the Association for support of studies to be conducted during the fiscal year beginning July 1, 1961. The deadline for applying for research fellowships and established investigatorships is September 15, 1960. Applications for grants-in-aid must be received by November 1, 1960.

Stipends in all categories have been increased this year based on the rising cost of living. Applications may be made for awards in the following categories.

Established Investigatorships: Usually awarded for five years, subject to annual review, in amounts from $7,500-$9,000 yearly plus dependency allowance, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. An additional grant of $500 is made to the investigator's department to assist in defraying the expense of his research program. Applicants may apply for grants-in-aid to support their research at the same time they apply for Established Investigatorships.

Advanced Research Fellowships: Awarded for periods of one or two years to postdoctoral applicants who have had some research training and experience but who are not clearly qualified to conduct their own independent research. During the second year of tenure they will be permitted to spend up to 25 per cent of their time in professional and scientific activities not strictly of a research nature, provided that these will contribute to their

professional development and do not involve services for a fee. These stipends range from $5,500 to $6,000 annually, plus dependency allowance. As in the case of Established Investigators, an additional grant of $500 is made to the investigator's department.

Research Fellowships: A limited number of awards are available to young men and women with doctoral degrees for periods of one or two years to enable them to train as investigators under experienced supervision. Annual stipends range from $4,500, plus dependency allowances. This type of award, however, is primarily made by local Heart Associations.

Grants-in-Aid: Made to qualified investigators to help underwrite the costs of specified projects.

Further information and application forms regarding research awards are obtainable from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N. Y.

List of Grants-In-Aid Awards

Following is the list of recipients of Grants-in-Aid awarded by the American Heart Association for the 1960-61 fiscal year, together with the subjects of their studies and the institutions at which they will be conducted.

New Approved Grants

Acheson, George H., M.D. Dihydrogenated cardiac glycosides. University of Cincinnati College of Medicine.

Alexander, Natalie, Ph.D. Observations and experimental studies on rabbits with inherited hypertension. Bunnyrun Rabbitry, Puente, Cal. and University of Southern California School of Medicine, Los Angeles.

Ambrus, Julian L., M.D., Ph.D. Fibrinolysin system. Roswell Park Memorial Institute, Buffalo, N.Y.

Bing, Richard J., M.D. Cardiac metabolism. Wayne State University College of Medicine, Detroit.

Bondurant, Stuart, M.D. Effect of central vascular engorgement on true pulmonary compliance. Indiana University School of Medicine, Indianapolis.

Bowman, Roger H., Ph.D. Normal and fasting metabolism of cardiac muscle and the hormonal influences involved. University of Cambridge, Cambridge, England.

Brewster, William R., Jr., M.D. Relationship of heart, striated and smooth muscle metabolism to function and mechanisms of their neuro-endocrine control. University of Florida College of Medicine, Gainesville.

Brown, David F., M.B., B.Ch. Role of triglyceride metabolism in ischemic heart disease. Cardiovascular Health Center, Albany Medical College, Albany N.Y.

Buckley, Nancy M., M.D. Cardiodynamics in valve disorders. Albert Einstein College of Medicine of Yeshiva University, New York, N.Y.

Chapman, Carleton B., M.D. Anatomic, physiological and experimental study of clubbing of the digits. University of Texas Southwestern Medical School, Dallas.

Clark, William G., Ph.D. Relation of function of cardiovascular system to the metabolism of catecholamines. Veterans Administration Center, Los Angeles, and Sepulveda Veterans Administration Hospital, Sepulveda, Cal.

Cohen, Louis, M.D. Phospholipid composition of serum lipoproteins and the coagulant activity of serum phospholipids in health and coronary artery disease. University of Chicago Clinics.

Conn, Hadley L., Jr., M.D. Myocardial metabolism; binding of quinidine to serum and cardiac proteins. University of Pennsylvania School of Medicine, Philadelphia.

Crismon, J. M., M.D. Regulation of nerve trunk blood supply; peripheral blood flow during nerve trunk ischemia. Stanford University School of Medicine, Stanford, Cal.

Csaky, T. Z., M.D. Uptake of sugars by the cardiac muscle. University of North Carolina School of Medicine, Chapel Hill.

Dammann, J. Francis, Jr., M.D. Serial evaluation of cardiopulmonary function following cardiac surgery. University of Virginia School of Medicine, Charlottesville.

Dennis, Clarence, M.D., Ph.D. Use of the heart-lung machine for support in myocardial infarction with shock. State University of New York Downstate Medical Center, Brooklyn, N.Y.

Dexter, Lewis, M.D. Mitral regurgitation and chamber volumes. Peter Bent Brigham Hospital, Boston.

Dunphy, J. Englebert, M.D. Occurrence, formation and metabolism of the fibrous protein of blood vessels, particularly the aorta. University of Oregon Medical School, Portland.

Edelman, Isidore S., M.D. Metabolic aspects of electrolyte transport. University of California School of Medicine, San Francisco.

Ederstrom, H. E., Ph.D. Mechanical characteristics of blood vessels after sympathectomy. University of North Dakota School of Medicine, Grand Forks.

Farber, Saul J., M.D. Lipid transport across the cell wall. New York University College of Medicine, New York, N.Y.

Fawaz, George, Ph.D., M.D. Effect of hormones o

the performance and metabolism of the isolated mammalian heart and on experimental arrhythmias. American University of Beirut School of Medicine, Beirut, Lebanon.

Fulkes, Ernest C., Ph.D. Control of intracellular electrolyte composition. May Institute for Medical Research of the Jewish Hospital Association, Cincinnati.

Freed, S. Charles, M.D. Possible role of excess norepinephrine secretion in the high incidence of essential hypertension found in subjects exhibiting a specific overt behaviour pattern. Harold Brunn Institute, Mount Zion Hospital and Medical Center, San Francisco.

Fresco, Jacques R., Ph.D. Macromolecular structure of enzymatically synthesized polynucleotides in relation to nucleic acid structure and function. Princeton University, Princeton, N.J.

Gidez, Lewis I., Ph.D. In vivo metabolism of long chain fatty acids. Albert Einstein College of Medicine of Yeshiva University, New York, N.Y.

Giebisch, Gerhard H., M.D. Ion transport across renal tubules of the mammalian and amphibian kidney utilizing micropuncture, microperfusion and microelectrode techniques. Cornell University Medical College, New York, N.Y.

Gonzales, I. Ernst, Ph.D. M.D. Comparative histochemical study of atherogenesis in human and experimental atherosclerosis. University of Alabama Medical Center, Birmingham.

Green, Harold D., M.D. Experimental studies in vasospastic and occlusive peripheral vascular diseases. Bowman Gray School of Medicine of Wake Forest College and North Carolina Baptist Hospital, Winston-Salem.

Green, Jack Peter, Ph.D., M.D. Relationship between heparin and amines in mast cells. Yale University School of Medicine, New Haven, Conn.

Grisolia, Santiago, M.D. Phosphoglycerate metabolism. University of Kansas Medical Center, Kansas City.

Guyton, Arthur C., M.D. Development and use of continuous recording instruments for cardiovascular research. University of Mississippi School of Medicine, Jackson.

Hawthorne, Edward W., M.D., Ph.D. Experimental hypertension: Part IV—Continuous and semicontinuous remote monitoring of the instantaneous changes in arterial pressure in dogs and primates developing experimental hypertension. Howard University College of Medicine, Washington, D.C.

Ingsted, D. Mark, Ph.D. Role of magnesium in atherosclerosis. Harvard University School of Public Health, Boston.

Isely, Walter S., M.D. Determination of myocardial blood flow in the intact subject utilizing radioiodinated (I^{131}) human serum albumin. Baylor University College of Medicine, Houston, Tex.

Heymann, Walter, M.D. Regulation of blood lipid concentration with special reference to pathogenesis of nephrotic hyperlipemia. Western Reserve University School of Medicine, Cleveland.

Hilton, James G., M.D. Adrenal gland physiology. St. Luke's Hospital, New York, N.Y.

Hume, Michael, M.D. Detection of intravascular thrombosis and treatment with thrombolytic agents. Yale University School of Medicine, New Haven, Conn.

Iseri, Lloyd T., M.D. Extracellular and cellular factors in congestive heart failure. Rancho Los Amigos Hospital, Downey, Cal.

Jedeikin, Lillian A., Ph.D. Myocardial metabolism in coronary insufficiency. Albert Einstein College of Medicine of Yeshiva University, New York, N.Y.

Jensen, David, Ph.D. Basic mechanisms of cardiac automatism. University of California, Scripps Institute of Oceanography, La Jolla, Cal.

Johnson, Paul C., Ph.D. Myogenic response of arterial vessels. Indiana University School of Medicine, Indianapolis.

Karnovsky, Manfred L., Ph.D. Physiological functions of polyenoic fatty acids. Harvard Medical School, Boston.

Katz, Yale J., Ph.D., M.D. Pyelonephritis. University of Southern California School of Medicine, Los Angeles.

Keys, Ancel, Ph.D. Epidemiology of heart disease. University of Minnesota School of Public Health, Minneapolis.

Kezdi, Paul, M.D. Function of the carotid sinus and hypothalamo-pituitary connections in experimental hypertension. Northwestern University Medical School, Chicago.

Khairallah, Philip A., M.D. Mechanism of action of vasopressor substances. Cleveland Clinic Foundation.

Kistin, Albert D., M.D. Analysis of clinical cardiac arrhythmias by means of simultaneous standard and esophageal leads for further study of multiple conduction pathways, retrograde conduction, reciprocal rhythm and characteristics of the A-V node. Beckley Memorial Hospital, Beckley, W. Va.

Kossman, Charles E., M.D., Med.Sc.D. Correlation of intracellular potentials of single cardiac fibers with mechanical function. New York University College of Medicine.

Kuhns, William J., M.D. Allergic reagin using the diphtheria system as a model. Central Blood Bank of Pittsburgh, University of Pittsburgh Health Center.

Kuo, Peter T., M.D., D.Sc. Effects, "clearing" and colloidal stability of serum triglycerides. University of Pennsylvania School of Medicine, Philadelphia.

Landowne, Milton, M.D. Pathophysiology of aortic

and peripheral vascular disorders. Levindale Hebrew Home and Infirmary, Baltimore.

Layne, Ennis C., Ph.D. Regulation of cholesterol synthesis in aortic tissue. University of Maryland School of Medicine, Baltimore.

Lazzarini, Abel A., Jr., M.D., Ph.D. Cytological studies on vascular changes on experimental and clinical diabetes mellitus. New York University Post-Graduate Medical School.

Lewis, David H., M.D. Application of underwater acoustics to the diagnosis of heart disease. Philadelphia General Hospital.

Lorber, Victor, M.D., Ph.D. Ions and heart muscle function. University of Minnesota Medical School, Minneapolis.

Lotspeich, William D., M.D. Relations between kidney metabolism and several of its excretory functions. University of Rochester School of Medicine and Dentistry, Rochester, N.Y.

Lundberg, Walter O., Ph.D. Lipid metabolism in relation to atherogenesis. Hormel Institute, University of Minnesota, Austin.

Mann, George V., Sc.D., M.D. Sterol secretion in bile and sulfur metabolism. Vanderbilt University School of Medicine, Nashville, Tenn.

Mathews, Martin B., Ph.D. Macromolecular structure and comparative biochemistry of connective tissue ground substance. LaRabida-University of Chicago Institute, LaRabida Jackson Park Sanitarium, Chicago.

McIntosh, Henry D., M.D. Importance of heart rate in adapting to circulatory stresses. Duke Medical Center, Durham, N.C.

Meilman, Edward, M.D. Collagen metabolism; isolation and characterization of urinary peptides containing hydroxyproline. Long Island Jewish Hospital, New Hyde Park, N.Y.

Mendlowitz, Milton, M.D. Digital circulation in hypertension; extension of inactivation of norepinephrine to secondary hypertension and to "toxemia" of pregnancy. Mt. Sinai Hospital, New York, N.Y.

Morris, George C., Jr., M.D. Renal revascularization for hypertension of renal vascular origin. Baylor University College of Medicine, Houston.

Murdaugh, Herschel V., Jr., M.D. Evaluation of stop-flow analysis through modification of technique. Medical College of Alabama, Birmingham.

Nelson, Russell M., M.D., Ph.D. Possible synergistic action on the heart between sodium chloride and the antifibrillatory drugs. Latter-day Saints Hospital, Salt Lake City, Utah.

Newburgh, R. W., Ph.D. Enzyme patterns in embryo and adult heart. Oregon State College, Corvallis, Ore.

Nyboer, Jan, Sc.D., M.D. Adaption of an aperiodic frictionless suspension for study of cardiorespiratory ballistics. Harper Hospital, Detroit.

Osborn, John J., M.D. Development of membrane oxygenators and other apparatus for cardiac surgery. San Francisco Institute of Medical Science, Stanford University Hospital.

Padawer, Jacques, Ph.D. Physiology and biochemistry of the mast cell in relation to cardiovascular function and disease. Albert Einstein College of Medicine of Yeshiva University, New York, N.Y.

Perry, H. Mitchell, Jr., M.D. Localization and effect of cadmium in mammalian tissues. Washington University School of Medicine, St. Louis.

Phillips, Gerald B., M.D. Individual phospholipids of human serum. Columbia University College of Physicians and Surgeons, New York, N.Y.

Pipberger, Hubert V., M.D. Analysis of phonocardiograms by digital computer. Georgetown University Hospital, Washington, D.C.

Pritchard, Jack A., M.D. Abnormalities in hemostasis during pregnancy. University of Texas Southwestern Medical School, Dallas.

Quick, Armand J., Ph.D., M.D. Relatonship of the clotting factor in erythrocytes to hemostasis and thrombosis. Marquette University School of Medicine, Milwaukee.

Rhinesmith, Herbert S., Ph.D. I. Chains in normal adult human hemoglobin; separation and amino acid sequence. II. Quantitative kinetic study of the dinitrophenylation of proteins. Allegheny College, Meadville. Pa.

Richmond, Jonas E., Ph.D. Role of the prosthetic group of proteins in the biosynthesis and metabolism of conjugated proteins. Harvard Medical School, Boston.

Robin, Eugene D., M.D. Changes in pulmonary gas exchange in clinical and experimental pulmonary embolism. University of Pittsburgh School of Medicine.

Ronwin, Edward, Ph.D. Enzymes involved in blood clotting and fibrinolysis; biochemical characterization of the processes. University of Minnesota College of Pharmacy, Minneapolis.

Rosenman, Ray H., M.D. Role of a specific overt behavior pattern in the prediction of clinical coronary heart disease. Harold Brunn Institute, Mount Zion Hospital and Medical Center, San Francisco.

Rushmer, Robert F., M.D. Distribution of blood flow in intact dogs. University of Washington School of Medicine, Seattle.

Rutstein, David D., M.D. Factors affecting lipoid deposition in human aortic cells in tissue culture. Harvard Medical School, Boston.

Sapirstein, Leo A., Ph.D., M.D. Cardiac output and its distribution in experimental hypertension. Ohio State University College of Medicine, Columbus.

Schwartz, Robert, M.D. Effects of salicylate on organic acid metabolism. Cleveland Metropolitan General Hospital.

Selkurt, Ewald E., Ph.D. Correlative stop-flow analysis

of renal blood flow and urine flow. Indiana University School of Medicine, Indianapolis.

Ellers, Alvin L., M.D. Metabolic pharmacological studies on the isolated, prefused mammalian kidney. Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles.

Hipp, Joseph C., M.D. Cell permeability and metabolism in the isolated, perfused rat heart. Harvard Medical School, Boston.

Humacker, Harris B., Jr., M.D. Inquiry into distribution of blood flow. Indiana University School of Medicine, Indianapolis.

Lumway, Norman E., M.D., Ph.D. Autotransplantation of the pulmonic valve. Stanford University School of Medicine, Palo Alto, Cal.

Singer, Thomas P., Ph.D. Electron transport mechanisms in heart and other tissues. Edsel B. Ford Institute for Medical Research, Henry Ford Hospital, Detroit.

Sirak, Howard D., M.D. Development of prosthetic valves for the human heart. Ohio State University College of Medicine, Columbus.

Spencer, Merrill P., M.D. Direct measurement of blood flow in humans. Bowman Gray School of Medicine of Wake Forest College and North Carolina Baptist Hospital, Winston-Salem.

Stefanini, Mario, M.D. Evaluaton of known and newly developed thrombolytic agents in animals and men with special reference to Aspergillin O (mold fibrinolysin). Saint Elizabeth's Hospital, Boston.

Swan, Henry, M.D., D.Sc. Development of adequate instrumentation for understanding and control of extracorporeal circulation. Halsted Experimental Surgical Laboratory, University of Colorado School of Medicine, Denver.

Swan, Roy C., M.D. Fine structure and electrical properties of frog lymph hearts. Cornell University Medical College, New York, N.Y.

Szent-Gyorgyi, Albert, M.D., Ph.D. Chemical macromolecular and histological structure of muscle and chemistry of contraction cycle; mechano-chemical coupling. Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Mass.

Takaro, Timothy, M.D., M.S. Development of techniques for the use of metallic clips and staples in large and small blood vessel anastomoses. Veterans Administration Hospital, Oteen, N.C.

Thomas, Lewis, M.D. Role of electrolytes and their relationship to extracellular and intracellular organic constituents in heart disease and other diseases producing edema. New York University College of Medicine.

Thompson, W. T., Jr., M.D. Gas exchange and the pulmonary capillary circulation. Medicl College of Virginia, Richmond.

Tobian, Louis, Jr., M.D. Pathogenesis of arterial hypertension. University of Minnesota Medical School, Minneapolis.

Towery, Beverly T., M.D. Renal and electrolyte metabolism. University of Louisville School of Medicine.

Von Korff, Richard W., Ph.D. Chemistry of fibrinogen, fibrinopeptides and related cold-insoluble clottable proteins. Variety Club Heart Hospital, University of Minnesota Medical School, Minneapolis.

Walker, Sheppard M., Ph.D. Automaticity and contractility of cardiac papillary muscle. University of Louisville School of Medicine.

Waters, Levin L., M.D. Modification of the lesions of experimental atherosclerosis. Yale University School of Medicine, New Haven, Conn.

Watts, Harvey F., M.D. Histochemical and physical chemical investigation of the role of connective tissue ground substance of the arterial intima in human coronary artery disease. Temple University Hospital, Philadelphia.

Welsh, Richard S., Ph.D. Characterization of undegraded, nonfibrous forms of desoxyribonucleoprotein from calf thymus. University of Redlands, Redlands, Cal.

Wesson, Laurence G., Jr., M.D. Diurnal cycle of renal function and electrolyte excretion in human essential hypertension. New York University Bellevue Medical Center.

Williams, Roger J., Ph.D. Role and site of binding of the metal ion in metal-containing or metal-activated enzymes. Clayton Foundation Biochemical Institute, University of Texas, Austin.

Willman, Vallee L., M.D. Fate of digitalis during extracorporeal circulation and elective cardiac arrest. Saint Louis University School of Medicine, St. Louis, Mo.

Wood, Francis C., M.D. Renal physiology, normal and pathological and energetics of the myocardium. Hospital of the University of Pennsylvania, Philadelphia.

Wood, Harrison F., M.D. Serological reaction obtainable between strains of group A streptococci and antiserum to normal human serum. Gaylord Hospital and Sanitorium, Wallingford, Conn.

Yang, William C. T., Ph.D. Effects of metal chelating agents on atrial fibrillation. University of Southern California School of Medicine, Los Angeles.

Continued Grants

Alfin-Slater, Roslyn B., Ph.D. Nutritional and metabolic studies on essential fatty acids. University of California, Los Angeles.

Berenson, Gerald S., M.D. Effect of inflammation on connective tissue. Louisiana State University School of Medicine, New Orleans.

Blumgart, Herrman L., M.D. Pathogenesis of intravascular thrombosis. Beth Israel Hospital, Boston.

Bohr, David F., M.D. Determinants of non-neurogenic vascular tone in normal and hypertensive animals. University of Michigan Medical School, Ann Arbor.

Booker, Walter M., Ph.D. Effect of some cardiac drugs on the heart during normothermia and hypothermia. Influence of cortisone and its congeners on heart action. Howard University College of Medicine, Washington, D.C.

Boyle, Edwin, Jr., M.D. Significance of intravascular agglutination of blood cells on microcirculation. Medical College of South Carolina, Charleston.

Brown, J. H. U., Ph.D. Metabolism of steroids in heart and kidney. Emory University School of Medicine, Atlanta.

Cayler, Glen G., M.D. Longitudinal study of hemodynamic and pulmonary vascular changes in the full-term and premature puppy. University of Oklahoma Medical School, Oklahoma City.

Clarkson, Thomas B., D.V.M. Chemotherapeutic studies on pigeon atherosclerosis. Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N.C.

Craige, Ernest, M.D. Left atrial pressure and pulmonary hypertension in patent ductus arteriosus. University of North Carolina School of Medicine, Chapel Hill.

Danowski, T. S., M.D. Application and assessment of hemodialysis and other forms of treatment in clinical and experimental renal insufficiency and the cardiovascular effects of such procedures. University of Pittsburgh School of Medicine.

Darby, Thomas D., Ph.D. Relations between acute cardiac failure, shock and acid-base rearrangements. Medical College of South Carolina, Charleston.

DeWall, Richard A., M.D. Perfusion techniques for reparative open intracardiac surgery. University of Minnesota Medical School, Minneapolis.

Dresel, Peter E., Ph.D. Automaticity in isolated preparations of cardiac muscle. University of Manitoba Faculty of Medicine, Winnipeg, Canada.

Elkinton, J. Russell, M.D. Clinical, physiological and biochemical studies of renal failure. University of Pennsylvania School of Medicine, Philadelphia.

Elwyn, David H., Ph.D. Relations between amino acid intake, tissue amino acid levels and turnover, and the rates of biosynthesis of proteins. Michael Reese Hospital and Medical Center, Chicago.

Enerson, Daniel M., M.D. Hepatic-blood flow and metabolism during extracorporeal circulation with the mechanical pump-oxygenator. State University of New York Upstate Medical Center, Syracuse, N.Y.

Epstein, Franklin H., M.D. Factors influencing renal concentrating ability. Yale University School of Medicine, New Haven, Conn.

Fishman, Alfred P., M.D. Interrelations between respiration and circulation in man. Columbia University College of Physicians and Surgeons, New York, N.Y.

Fregly, Melvin J., Ph.D. Regulation of sodium intake by hypertensive rats. University of Florida College of Medicine, Gainesville.

Friedman, Meyer, M.D. Further studies concerning the metabolism of cholesterol. Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital and Medical Center, San Francisco.

Gibbon, John H., Jr., M.D. Physiological study of myocardial changes in induced cardiac arrest. Jefferson Medical College of Philadelphia.

Gibson, David M., M.D. Role of biotin in the biosynthesis of fatty acids. Indiana University Medical School, Indianapolis.

Glover, Robert P., M.D. Experimental evaluation of surgical methods for treatment of coronary insufficiency. Presbyterian Hospital, Philadelphia.

Good, Robert A., M.D., Ph.D. Continued study of basic mechanisms involved in pathogenesis of rheumatic fever and other cardiovascular-renal diseases. University of Minnesota Medical School, Minneapolis.

Goodyer, Allan V. N., M.D. Extracardiac determinants of ventricular competence and myocardial metabolism in the intact animal. Yale University School of Medicine, New Haven, Conn.

Gottschalk, Carl W., M.D. Micropuncture study of kidney function. University of North Carolina School of Medicine, Chapel Hill.

Griesemer, Robert D., M.D. Lipid metabolism in the skin. Massachusetts General Hospital, Boston.

Gross, Robert E., M.D. Studies relevant to surgical treatment of congenital heart disease. Children's Hospital, Boston.

Guze, Lucien B., M.D. Observations on the association of hypertension and experimental pyelonephritis. University of California at Los Angeles School of Medicine.

Havel, Richard J., M.D. Mechanisms and control of fatty acid transport and metabolism. University of California School of Medicine, San Francisco.

Hirschhorn, Kurt, M.D., M.S. Genetic and metabolic study of familial hyperlipemia. New York University Post-Graduate Medical School.

Hoffman, Brian F., M.D. Electrophysiology of cardiac muscle. State University of New York Downstate Medical Center, Brooklyn, N.Y.

Holland, William C., M.D. Mode of action of antiarrhythmic agents. University of Mississippi Medical Center, Jackson.

Hook, Edward W., M.D. Host factors in experimental streptococcal infection. Cornell University Medical College, New York, N.Y.

Howard, John M., M.D. Anatomy and function of normal and pathological lymph vessels by radiographic and isotopic techniques. Hahnemann Medical College and Hospital, Philadelphia.

Johnson, Alan J., M.D. Enzyme studies and coagulation research. New York University Bellevue Medical Center.

Kaplan, Samuel, M.D. Myocardial oxygen tension. Children's Hospital Research Foundation, Cincinnati.

Katz, Louis N., M.D. Metabolic and hemodynamic interrelationships in the intact myocardium. Medical Research Institute, Michael Reese Hospital, Chicago.

Kerby, Grace P., M.D. Metabolism of acid mucopolysaccharides of ground substance. Duke University School of Medicine, Durham, N.C.

Keys, Ancel, Ph.D. Effect of diet on blood serum cholesterol and lipoproteins in man. University of Minnesota School of Public Health, Minneapolis.

Koelle, George B., Ph.D., M.D. Physiology and pharmacology of the coronary circulation with special reference to intercoronary reflexes and their relation to myocardial metabolism. University of Pennsylvania School of Medicine, Philadelphia.

Krayer, Otto, M.D. Further studies on the circulatory action of the Rauwolfia alkaloids. Harvard Medical School, Boston.

Kuida, Hiroshi, M.D. Pressure-volume relationships of the pulmonary circulation; the significance of the left atrial-pulmonary venous system as a volume receptor. University of Utah College of Medicine, Salt Lake City.

LaBella, Frank S., Ph.D. Biochemistry of elastic tissue. University of Manitoba Faculty of Medicine, Winnipeg, Canada.

LaDue, John S., M.D., Ph.D. Electrocardiogram during physical exercise. Sloan-Kettering Institute for Cancer Research, New York, N.Y.

Lathem, Willoughby, M.D. Mechanism of proteinuria and characterization of the glomerular membrane defect in renal disease. University of Pittsburgh School of Medicine.

Leaf, Alexander, M.D. Renal acidifying mechanisms. Massachusetts General Hospital, Boston.

Leiter, Louis, M.D., Ph.D. Role of body electrolyte content in the response to drug therapy of hypertension. Montefiore Hospital, New York, N.Y.

Levy, Robert S., Ph.D. Enzymatic activity on natural and synthetic substrates of lipoprotein lipase from tissue and plasma. University of Louisville School of Medicine.

Liebelt, Robert A., Ph.D., M.D. Effect of the adrenal gland on obesity in mice. Baylor University College of Medicine, Houston, Tex.

Lilienfield, Lawrence S., M.D., Ph.D. Intrarenal circulation. Georgetown University Medical Center, Washington, D.C.

Little, J. Maxwell, Ph.D. Relationships between mixed venous pO_2 and adrenal cortical activity and cardiodynamics. Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N.C.

Little, Robert C., M.D. Effect of variable right ventricular stress on the dynamics of the left ventricle. Seton Hall College of Medicine and Dentistry, Jersey City, N.J.

Lukas, Daniel S., M.D. Quantitation of valvular regurgitation. Cornell University Medical College, New York, N.Y.

Mallov, Samuel, Ph.D. Tissue lipoprotein lipase. Research Foundation of State University of New York, Syracuse, N.Y.

Mayerson, H. S., Ph.D. Permeability of lymphatic vessels. Tulane University School of Medicine, New Orleans.

McDonald, Joseph J., M.D. Rheumatic and congenital heart diseases in the Middle East. American University of Beirut School of Medicine, Beirut, Lebanon.

Meiklejohn, Gordon, M.D. Fibrinolytic enzymes. University of Colorado School of Medicine, Denver.

Meng, H. C., M.D., Ph.D. Production of lipemia clearing factor and its inhibitor and their role in lipid metabolism and atherogenesis. Vanderbilt University School of Medicine, Nashville, Tenn.

Miller, Benjamin F., M.D. Arteriosclerosis in the rat. May Institute for Medical Research of the Jewish Hospital Association, Cincinnati.

Milnor, William R., M.D. Relationships between pulmonary vascular resistance and pulmonary blood volume. Johns Hopkins Hospital, Baltimore.

Moe, Gordon K., M.D., Ph.D. Nature of atrial fibrillation. Masonic Medical Research Laboratory, Utica, N.Y.

Montgomery, Hugh, M.D. Oxygen tension of muscle. Hospital of the University of Pennsylvania, Philadelphia.

Olson, Robert E., M.D. Effect of congestive heart failure due to valvular disease upon the contractile proteins in dogs and man. University of Pittsburgh Graduate School of Public Health.

Paul, Oglesby, M.D. Longitudinal study of coronary heart disease. Presbyterian-St.Luke's Hospital, Chicago.

Perry, H. Mitchell, Jr., M.D. Relation of trace metals to atherosclerosis. Washington University School of Medicine, St. Louis.

Porter, John W., Ph.D. Mechanism of the enzymatic synthesis of fatty acids. University of Wisconsin, Madison.

Ratnoff, Oscar D., M.D. Initiation of blood coagulation. Western Reserve University School of Medicine, Cleveland.

Rodbard, Simon, M.D., Ph.D. Role of mechanical tension (pressure X radius) in myocardial dynamics. University of Buffalo Chronic Disease Research Institute, Buffalo, N.Y.

Sanford, Jay P., M.D. Relationship of inapparent pyelonephritis to arterial hypertension. University of Texas Southwestern Medical School, Dallas.

Sawyer, Philip N., M.D. Bioelectric phenomena and intravascular thrombosis. State University of New York Downstate Medical Center, Brooklyn, N.Y.

Schlant, Robert C., M.D. Use of thermistors as flowmeters. Emory University School of Medicine, Atlanta.

Schmidt-Nielsen, Bodil, D.D.S., D.Odont., D.Phil. Renal mechanism for urea and salt excretion. Duke University, Durham, N.C.

Seaman, Arthur J., M.D. Controlled long-term study of continuous anticoagulant therapy in coronary artery disease. University of Oregon Medical School, Portland.

Siegal, Alan C., M.D. Group A streptococcal infections in children, with particular reference to the attack rate and prevention of rheumatic fever. Children's Memorial Hospital, Chicago.

Siperstein, Marvin D., M.D., Ph.D. Factors influencing the excretion and synthesis of cholesterol. University of Texas Southwestern Medical School, Dallas.

Smith, Richard T., M.D. Ontogeny of inflammatory and immune responses. University of Florida College of Medicine, Gainesville.

Stamler, Jeremiah, M.D. Assessment of ability to prevent clinical coronary heart disease by nutritional means in high-risk middle-aged males. Chicago Board of Health.

Starzl, Thomas E., M.D. I. Surgical therapy of aortic insufficiency. II. Treatment of cerebral edema due to anoxia. Northwestern University Medical School, Chicago.

Szent-Gyorgyi, Andrew G., M.D. Structure of the contractile proteins and chemistry of contraction. Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Mass.

Taylor, C. Bruce, M.D. Human cholesterol metabolism and its relationship to atherosclerosis. Evanston Hospital Association, Evanston, Ill.

Taylor, Henry L., Ph.D. Death rates and physical activity among railroad workers with special reference to coronary heart disease in middle-aged men. University of Minnesota School of Public Health, Minneapolis.

Threefoot, Sam A., M.D. Direct observation of vascular channels, capillary beds and lymphatics of the intact human male. Touro Infirmary, New Orleans.

von Kaulla, Kurt N., M.D. Fibrinolytic enzymes. University of Colorado School of Medicine, Denver.

Wartman, William B., M.D. Response of endothelial cells to injury. Northwestern University Medical School, Chicago.

Watson, Cecil J., M.D. Fatty acids and atherosclerosis. University of Minnesota Medical School, Minneapolis.

Webb, J. Leyden, Ph.D. Effects of cardioactive drugs on atrial membrane potentials and contractility. University of Southern California School of Medicine, Los Angeles.

Wégria, René, M.D. Coronary circulation and cardiac metabolism under normal and pathological conditions. Saint Louis University School of Medicine, St. Louis.

Weil, Max H., M.D., Ph.D. Effect of head down position on the efficiency of circulation in the presence of shock. University California School of Medicine, Los Angeles.

Weller, John M., M.D. Investigation of abnormalities of electrolyte metabolism in hypertension. University of Michigan Medical School, Ann Arbor.

Welt, Louis G., M.D. Evaluation of the usefulness of extracorporeal hemodialysis in the management of chronic renal insufficiency. University of North Carolina School of Medicine, Chapel Hill.

Wessler, Stanford, M.D. Intravascular thrombosis. Beth Israel Hospital, Boston.

Wesson, Laurence G., Jr., M.D. Mechanisms of sodium chloride excretion. New York University Post-Graduate Medical School.

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